UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Court File No.: 2:15-cv-01202-WCB **JURY TRIAL DEMANDED**

DEFENDANT ELI LILLY & COMPANY'S
MOTION FOR JUDGMENT AS A MATTER OF LAW OR,
IN THE ALTERNATIVE, A NEW TRIAL

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Defendant Eli Lilly and Company, pursuant to Fed. R. Civ. P. 50(b), hereby renews its motion for judgment as a matter of law ("JMOL") that claim 1 of U.S. Patent No. 8,791,124 ("the '124 patent") is invalid and alternatively moves for a new trial under Fed. R. Civ. P. 59.

I. INTRODUCTION

The field of biotechnology has been plagued from its inception by attempts to preempt valuable future developments based on prematurely filed patent applications. Researchers have repeatedly posited what they believe to be a natural, underlying mechanism of a human disease state and then attempted to preempt future developments in that field by prematurely patenting methods of using ***all molecules*** that function to disrupt that identified natural mechanism. The traditional tools of the patent statute have evolved to prevent such attempts to reap where the alleged inventor has not yet sown. The law regarding patent eligibility under 35 U.S.C. § 101 has been applied to foreclose attempts to patent what are in essence simply discoveries of natural laws and mechanisms. The written description requirement of 35 U.S.C. § 112 has been construed to prohibit attempts to preempt the future before it has arrived by patenting use of unknowably large numbers of undescribed compounds identified only by their functional ability to interfere with a natural disease process. Similarly, the enablement requirement of 35 U.S.C. § 112 has been construed in such cases to prohibit claims that are, in essence, invitations to engage in extensive and unpredictable experimentation in order to identify useful molecules by sifting through large numbers of candidate molecules that have been claimed solely by their function. So clear are such classic failures to comply with the disclosure requirements of the Patent Law that they are frequently resolved on motions for summary judgment or JMOL based on review of the four corners of the patent text. This is just such a case: judgment as a matter of law should be entered in Lilly's favor that the asserted claim 1 of the '124 patent is invalid.

Here, the UroPep researchers allege they discovered an unpatentable Law of Nature, specifically that three phosphodiesterase enzymes—PDE I, PDE IV, and PDE V—are of "particular importance" in the prostatic muscle. ('124 Pat., col. 2:6-8.) In an apparent attempt nonetheless to preempt future developments based on that alleged discovery, UroPep filed a patent application in July 1997 prophetically describing a purported "effective" human treatment of a diverse spectrum of conditions implicating not only the prostate but also the bladder and penis, using "selective inhibitors of PDE I, IV and V." (*Id*., col. 2:17-28.) The original application text merely lists two enormous classes of compounds and ten compounds with eclectic structures ***without*** identifying any such compound as being "selective" for ***any*** particular PDE, ***without*** identifying which of the innumerable number of compounds within the two classes inhibit ***any*** particular PDE, and ***without*** linking such structurally diverse compounds to the treatment of ***any*** specific condition. Moreover, nowhere in the original application text is "PDE V" identified as having any particular importance (compared to PDE I or PDE IV) in the treatment of any disease. In essence, the application invited continued experimentation to figure out which combinations of inhibition of "PDE I, IV and V" were important for each condition and to discover those molecules capable of effectively inhibiting that combination.

After abandoning the original application, a continuation application was filed that led to issuance of U.S. Patent No. 8,106,061 ("the '061 patent"), which claimed the use of "selective inhibitors of PDE IV and/or V" selected from the compounds specifically enumerated in the specification. However, the particular importance of selective inhibition of PDE V, to the exclusion of PDE I and IV, in specific treatment of the ill-defined and hard-to-treat BPH condition, became apparent to UroPep only in 2011, when Lilly received FDA approval to market Cialis® (tadalafil), at a specific dose and by a specific route of administration, for the

treatment of the signs and symptoms of BPH. But the claims in UroPep's parent '061 patent, did not cover tadalafil; nor is tadalafil mentioned in the application text. In a thinly veiled attempt to reap where it had not sown, UroPep went back to the U.S. Patent and Trademark Office (PTO) in late December 2011 and filed a "continuation" application seeking newly crafted claims that would encompass Lilly's Cialis® BPH indication. That effort led to the issuance in 2014 of claim 1 of the '124 patent, which claims an entirely different invention from that described in the original application. Gone is the blunderbuss disclosure of treating a broad spectrum of diseases and with undifferentiated inhibitors of PDE I, IV, and V—replaced by a previously undescribed specific method of treating only BPH with just a "selective" PDE V inhibitor. Also gone are the limitations to the compounds actually described and claimed in the original application, replaced by an asserted right to exclude prophylaxis or treatment of BPH by the use of ***any*** compound, of any type, size, structure, and class, based solely on its function of selectively inhibiting PDE V.

Inspection of the four corners of the '124 patent establishes that claim 1 violates the written description requirement in at least two well-recognized respects. First, these patentees have selectively plucked individual elements from an earlier filed generic disclosure and later recombined them in a single claim to cover specifically the subsequent and previously undescribed invention of Lilly without any blaze marks within the four corners of the patent document indicating that such a specific subcombination was ever contemplated by the inventors at the time of original filing. (§ IV.B., *infra*.) Second, these patentees sought to preempt the future before it had arrived by claiming treatment and prophylaxis of BPH with a massive and unbound genus of molecules defined ***solely*** by what they do (selectively inhibit PDE V) rather than by what they are. It has been repeatedly held that, in the latter circumstance, a legally adequate written description requires either enumeration in the specification of a representative

number of species falling within the claimed genus to illustrate possession of its full scope, or the disclosure of a correlation between the chemical structure of the members of the genus and the claimed function. This patent specification contains neither. Indeed, all but two of the molecules specifically disclosed in the specification have been explicitly ***excluded*** from the claim and cannot, therefore, illustrate its scope. The remaining two are not described in the specification as being selective PDE V inhibitors as required by this claim, and certainly cannot support the vast weight of the potentially many billions of undescribed, structurally diverse molecules prophesized to inhibit PDE V potentially falling within the scope of the claim. (§ IV.C., *infra*.)

Further, these patentees also violated the enablement requirement as a matter of law in that they sought to claim all methods of ***effectively*** treating and prophylacting the ill-defined disease known as BPH in humans, using an enormous number of ill-defined and undescribed "selective" inhibitors, where it was established that: (1) the disclosed method of assessing PDE V selectivity was deficient; (2) selectivity alone does not predict ***effective*** human treatment, (3) potency also does not predict ***efficacy*** (additional factors, such as bioavailability, absorption, metabolism, etc. are required); and (4) a person skilled in the art, therefore, could not tell whether any particular compound could be used effectively without testing it. Binding precedent recognizes that such unguided invitations to experiment do not satisfy the enablement requirement across the breadth of the claim as a matter of law. (§ V., *infra*.)

The inadequacy of the written description and enabling disclosure in the '124 patent have legal consequences under other statutory requirements of the patent law. Inadequacies of the disclosed method of determining PDE V selectivity renders the claims invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2. (§ VI., *infra*.) In addition, if the mere germ of an idea described in the '124 patent is deemed legally adequate, the conclusion would then be compelled that the

claimed invention would have been invalid for obviousness from prior art that showed at least as much of this invention as the patentees disclosed. (§ VII., *infra*.) Similarly, if this patent's dearth of guidance regarding identification of "effective" doses is adequate, then reported positive results with treatment of BPH with herbal remedies containing a selective PDE V inhibitor (icariin) anticipate the claim under 35 U.S.C.§ 102. (§ VIII., *infra*.)

For these and for the reasons set forth more fully below, JMOL should be entered that claim 1 of the '124 patent is invalid. At a minimum, a new trial is warranted as the verdicts on these issues are against the clear weight of the evidence or the result of erroneous jury instructions or evidentiary rulings. (§§ IX-XV., *infra*.)

II. LEGAL STANDARDS APPLICABLE TO JMOL AND A NEW TRIAL

Judgment as a matter of law is proper if the Court finds that "a reasonable jury would not have a legally sufficient evidentiary basis to find for the party on that issue." *Centocor Ortho Biotech, Inc. v. Abbott Labs.,* 636 F.3d 1341, 1347 (Fed. Cir. 2011) (citing *Cambridge Toxicology Grp., Inc. v. Exnicios*, 495 F.3d 169, 179 (5th Cir. 2007) (quoting Fed. R. Civ. P. 50(a)(1)). A post-trial motion for JMOL may be granted when the facts and inferences so conclusively favor one party "that reasonable jurors could not arrive at a contrary verdict." *TGIP, Inc. v. AT&T Corp.*, 527 F. Supp. 2d 561, 569 (E.D. Tex. 2007) (quoting *Tol-O-Matic, Inc. v. Proma Produkt–Und Mktg. Gesellschaft m.b.H.*, 945 F.2d 1546, 1549 (Fed. Cir. 1991)).

With specific reference to the written description and enablement requirements, and as noted above, there are recurring fact patterns that lead inexorably to a determination of the legal insufficiency of the supporting description from review of the four corners of the patent specification. These include attempts to claim methods of treatment using large and structurally undefined classes of compounds defined, as here, not by what they are but only by a function

they perform. *Ariad Pharms., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc) (JMOL of invalidity under written description requirement); *see also Centocor*, 636 F.3d at 1352-53 (reversing district court's denial of JMOL and finding that asserted claims failed to satisfy written description requirement). They also include belated attempts—like that at issue here—to carve out of a worthlessly broad disclosure claims to a narrower, undescribed specific embodiment shown to be valuable by the subsequent efforts of others. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346 (Fed. Cir. 2013) (affirming district court's grant of JMOL of invalidity under written description requirement). With specific regard to enablement, the recurring fact pattern manifest here of attempting to patent the fruit of what at best represents a research plan also supports summary determination of invalidity for lack of enablement as a matter of law. *Wyeth v. Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013).

Further, a new trial is plainly warranted here as the jury verdict was "clearly contrary to the weight of the evidence." *Smith v. Transworld Drilling Co.*, 773 F.2d 610, 613 (5th Cir. 1985). In making this determination, the Court "weighs all the evidence, but need not view it in the light most favorable to the nonmoving party." *Id*. "If the trial judge is not satisfied with the verdict of a jury, he has the right—and indeed the duty—to set the verdict aside and order a new trial." *Id*.

III. OVERVIEW OF THE '124 PATENT

The '124 patent issued on July 29, 2014 from application No. 13/339,561 filed on December 29, 2011, a few months after Lilly obtained approval from the FDA to market Cialis® (tadalafil) at an oral dosage of 5 mg, once per day, for treatment of the signs and symptoms of BPH. The application for the '124 patent was filed as a "continuation" of application No. 10/443,870 filed on May 23, 2003, which had resulted in the '061 patent, issued January 31,

2012 (PX 193). The application for the '061 patent was itself a "continuation" of application No. 09/462,090, first filed on July 9, 1997 as a PCT application, No. PCT/EP97/03617. The '124 patent claims priority to the original July 9, 1997 disclosure.

The original 1997 patent application was predicated on the alleged discovery that three different PDEs (PDE I, IV, and V) are of "particular importance in the human prostatic muscle." ('124 Pat., col. 2:6-11.) That discovery plainly constitutes an unpatentable law of nature. *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015). As such, the inventors sought to claim something else. The original patent specification thus offered the prophetic hypothesis that inhibition of all three enzymes might treat a ***wide variety of conditions*** affecting the prostate, bladder, and penis, including among many others BPH. ('124 Pat., col. 2:11-28.) Diseases mentioned include "prostatic diseases, in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles, [and] impotence." (*Id.*, col. 2:17-24.)

That the invention contemplated at the time of the original filing had not focused on use of a selective PDE V inhibitor alone to treat just BPH is manifest from the original claims, which did ***not*** mention inhibition of any PDE—much less PDE V—but instead claimed generic methods of treating all disclosed conditions with any of the specifically disclosed compounds. (DX 1004 at p. JX_061_FH0024-35) (original claims 1-3). The original application was abandoned and the continuation application that led to the '061 patent was filed. In prosecuting the '061 patent application, UroPep canceled those original claims (DX 1004 at p. JX_061_FH0004) and instead sought claims to selective inhibitors of PDE IV and/or PDE V. As issued, the '061 patent has two independent claims, each ***limited*** to the use of "a selective

inhibitor of phosphodiesterase IV and/or phosphodiesterase V" selected from a group consisting of the compounds that were ***expressly*** disclosed in the original application text as "selective inhibitors of PDE I, IV and V." (PX 193, '061 Pat., col. 8:4-26, 29-54.)

Unlike the claims of the parent '061 patent, claim 1 of the '124 patent is not limited to the use of any specific compound, whether by chemical name, structure, or class. Rather, claim 1 of the '124 patent encompasses the administration of "an inhibitor of phosphodiesterase (PDE) V"—construed by the Court to mean ***any compound*** that selectively inhibits PDE V at least 20 times more effectively than PDE I through PDE IV—that can be delivered in an effective amount for the prophylaxis or treatment of BPH. As noted, none of the disclosed compounds are identified specifically as a "selective" inhibitor of PDE V. The specification cites two papers as disclosing "known methods" to determine whether a compound "is suitable for the purpose according to the invention, i.e. is an inhibitor of sPDE I, IV or V" ('124 pat., col. 7:35-39) and a third paper by the UroPep researchers for the "determination of sPDE" (*id.*, col. 7:39-45, the "Truss" paper). However, the evidence at trial was that none of these papers actually determined any compound to be a "selective" inhibitor of PDE V, and the Truss paper was shown at trial, without rebuttal, to be incapable of doing so. (§ V.D., *infra*.)

In addition, claim 1 clearly states that just identifying a compound that selectively inhibits PDE V is not enough. Rather, the claim further requires administration of an "effective amount" of any and all selective PDE V inhibitors to a "person" in need of, and for the purpose of, "prophylaxis or treatment of benign prostatic hyperplasia." Yet, the specification leaves identification of "effective" compounds and "effective" doses thereof to subsequent experimentation by others, based on the "species, body weight, age, individual condition, and kind of administration." ('124 pat., col. 5:1-3). And, while the specification provides a broad,

nearly 10,000-fold range of "0.15 µg to 1 mg" for administration by ***parenteral*** administration (*id.*, col. 5:8-9), it is silent about other routes of administration (including oral doses) and fails to inform the skilled artisan how to achieve effectiveness in BPH for any specific inhibitor let alone all inhibitors of PDE V. Indeed, the specification's discussion of the organ bath test to ascertain smooth muscle relaxation is not specific to any compound or to any inhibitor of PDE I, IV and V. (*Id.*, col. 7:14-34, stating: "In these studies, the ***inhibitors of PDE I, IV and V*** proved to have the strongest prostatic relaxing effect." (emphasis added)). Further, the specification does not differentiate any "effective amount" as between inhibitors of sPDE I, IV and V. (*Id.*, col. 4:65-67.) In sum, out of the billions of potential PDE V inhibitors, the '124 patent provides no guidance, by working example or otherwise, in determining which selective PDE V inhibitors will actually work in the claimed method.

IV. CLAIM 1 OF THE '124 PATENT IS INVALID AS A MATTER OF LAW FOR FAILURE TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT

A. The Written Description Requirement

Title 35 U.S.C. § 112 codifies the bargain between the public and the inventor that underlies our patent system. In exchange for the right to exclude all others from practicing the claimed invention, § 112 mandates that the patent provide a description of the invention. *Ariad*, 598 F.3d at 1354 (explaining that the obligation to describe one's invention "is part of the *quid pro quo*" of obtaining a patent). This requirement, referred to as the "written description requirement," ensures that the inventor includes enough description in the specification of a patent to demonstrate that the inventor actually invented and was in possession of what has been claimed. "Patents are not awarded for academic theories, no matter how groundbreaking or necessary to the later patentable inventions of others." *Id.* at 1353. As set forth by the *en banc*

Federal Circuit: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Id.* (alteration in original) (quoting *Univ. of Rochester v. G.D. Searle & Co*., 358 F.3d 916, 930 n.10 (Fed. Cir. 2004). "Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'—that is, conceive of the complete and final invention with all its claimed limitations—and disclose the fruits of that effort to the public." *Ariad*, 598 F.3d at 1353. "Although the content varies, the threshold in all cases requires a transition from theory to practice, from basic science to its application, from research plan to demonstrated utility." *Id.* at 1359 (Newman, J., concurring).

Further, in judging the adequacy of the written description, courts examine the "***the four corners of the specification*** from the perspective of a person of ordinary skill in the art." *Ariad,* 598 F.3d at 1351 (emphasis added). Thus, to meet the written description requirement, the specification itself, within its four corners, "must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Id.* "[A]ctual 'possession' or reduction to practice outside of the specification is not enough. Rather, . . . it is the specification itself that must demonstrate possession." *Id.* at 1352. As a result, courts have routinely decided the written description issue upon motions for summary judgment or on motions for JMOL following a jury verdict. *Id.* at 1358 (reversing denial of Lilly's JMOL motion); *see also Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367-69 (Fed. Cir. 2011) (affirming summary judgment of invalidity); *Centocor*, 636 F.3d at 1353 (reversing denial of Abbott's JMOL motion and stating that "[a] patent also can be held invalid for failure to meet the written description requirement based solely on the face of the patent specification."); *Rochester,* 358 F.3d at 929-30 (affirming summary judgment); *Carnegie Mellon*

Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1128 (Fed. Cir. 2008) (affirming summary judgment of invalidity).

Throughout the decades, courts have noted different types of defects that can occur in the written description of patents. One recurring type of defect arises when an original specification describes an invention generically then, some years later, the inventor adds claims to a subpart of that genus to capture intervening developments of others. Where the importance and value of this narrower invention was not recognized or described in the original disclosure, the written description requirement is violated. *See Novozymes*, 723 F.3d at 1344; *In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A. 1967). In such cases, the Federal Circuit requires that the original specification contain "blaze marks" as objective indications that the inventor was actually in possession of the later claimed subject matter at the time of the ***original*** application. *Ruschig*, 379 F.2d at 994-95; *see also Boston Scientific*, 647 F.3d at 1367-69; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996).

A second recurring type of defect arises when the claims, either original or later added, use overly broad functional language but the specification fails to provide a description of the actual molecules that can accomplish the claimed function. This is the problem that existed in cases such as *Ariad,* 598 F.3d at 1352, and *Rochester*, 358 F.3d at 929-30. These cases make clear that a patent claim that recites a genus of compounds described merely by their function—as does claim 1 of the '124 patent—must be supported by a written description that discloses ***sufficient representative*** species within the claimed genus or "structural features ***common to members of the genus*** so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (citation omitted) (emphasis added). Thus, "functional claim language can meet the written description requirement when the art has established ***a correlation***

between structure and function." *Id*. (emphasis added). "But merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Id*. And black-letter precedent of the Federal Circuit mandates that that this requirement applies whether the claim is to the genus itself ***or*** to the use of the genus ***in a method of treatment claim***. *E.g.*, *id.* at 1349-50; *Boston Scientific*, 647 F.3d at 1363; *In re Alonso*, 545 F.3d 1015, 1019 (Fed. Cir. 2008); *Rochester*, 358 F.3d at 927-29.

As discussed below, the '124 patent suffers from ***both*** of these written description defects and runs afoul of more than forty years of binding precedent.

B. The Generic Disclosure In the '124 Patent Does Not Provide Adequate Support for the Narrowed Invention of Claim 1 as a Matter of Law

It has been settled law for decades that when claims are added later in time during prosecution, the written description in the ***original application*** must provide sufficient detail to identify and describe the inventions later claimed. *Schriber-Schroth Co. v. Cleveland Trust Co*., 305 U.S. 47, 57-59 (1938); *Ruschig*, 379 F.2d at 995; *Fujikawa*, 93 F.3d at 1570; *Ariad*, 598 F.3d at 1363 (Rader, J., dissenting-in-part, concurring-in-part); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). As reflected in the cited cases, this problem is particularly acute where the specification discloses generic subject matter, without any recognition of the importance of a particular narrower embodiment or sub-genus of that genus, yet claims are later presented seeking to carve out of that genus such an undescribed narrower sub-genus.

In such cases, the court looks for "blaze marks" in the original text leading the way to this latter claimed subject matter, just as blaze marks on trees show the path to be followed in the woods. As described in *Ruschig*, "[i]t is an old custom in the woods to mark trails by making *blaze marks* on the trees. It is no help in finding a trail or in finding one's way through the woods

where the trails have disappeared—or have not yet been made, which is more like the case here—to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none." 379 F.2d at 994-95. This was also the fact pattern in In *Boston Scientific*, where the Federal Circuit noted a lack of "blaze marks" and explained that "[h]ere, the inventors similarly disclosed a genus (analogs of rapamycin), but claimed a ***narrower*** sub-genus (macrocyclic triene analogs of rapamycin). However, nothing in the '662 patent indicates that the claimed triene analogs might be of special interest." 647 F.3d at 1367 (emphasis added); *see also Fujikawa*, 93 F.3d at 1571.

Finally, *Novozymes* involved circumstances where the original specification described a genus of compounds that may or not work but the later issued patent sought to narrow that genus based on the work of a competitor in discovering that a particular subgenus of compounds was actually successful. 723 F.3d at 1348-50. The Federal Circuit rejected Novozyme's attempt, explaining that Novozyme's original application, "[a]t best . . . describes a roadmap for producing candidate alpha-amylase variants and then determining which might exhibit enhanced thermostability." *Id.* at 1350. But, according to the court, a patent "'is not a reward for the search, but compensation for its successful conclusion.' For that reason, the written description requirement prohibits a patentee from 'leaving it to the . . . industry to complete an unfinished invention.'" *Id.* (quoting *Ariad*, 598 F.3d at 1353 (quoting *Rochester*, 358 F.3d at 930 n.10)).

This authority compels the invalidity of claim 1 of the '124 patent. The original application for the '124 patent purports to identify "[p]referred selective inhibitors of PDE I, IV and V" without any distinction in any way (1) between inhibiting these three distinct PDEs or (2) as to which inhibitors were "effective" against which diseases. (*See* § III., *supra*.) Nowhere in the original disclosure was the use of a selective PDE V inhibitor alone for treatment of just BPH

recognized as important in any way. It was ***Lilly scientists***—not the UroPep researchers—who established through initial proof-of-concept testing and subsequent controlled dosing and efficacy studies that the selective PDE V inhibitor tadalafil is actually effective at a specific dose to treat the signs and symptoms of BPH. Nevertheless, the claim 1 of the '124 patent was manifestly intended to capture that later-proven, more-specific concept even though the original application text was completely devoid of any "blaze marks" indicating that the patentees were ever in possession of this specific concept. As previously noted, the '124 patent does not link any of the disclosed compounds to inhibiting PDE I versus PDE IV versus PDE V, as admitted by Dr. Bell. (Tr. 1306:21-1307:8.) And nothing in the '124 patent's disclosure indicates that PDE V might be of special interest compared to PDE I or PDE IV. As previously pointed out by this Court, the specification of the '124 patent also "provides no suggestion as to why a person of ordinary skill would single out PDE V rather than the other two PDE inhibitors of interest, PDE I and PDE IV." (Mem. Op. & Order, Dkt. 149 at 35.)

As in *Novozymes*, the purported invention of the '124 patent was incomplete, leaving it to the industry to finish it. Dr. Bell explicitly testified that the '124 patent is actually "a method of enabling the discovery of new drugs." (Tr. 1323:11-14.) Dr. Uckert himself characterized the "work" that the inventors allegedly did and disclosed in the patent as a "research plan." (Tr. 162:3-15.) Indeed, at most, the inventors of the '124 patent identified PDE I, PDE IV and PDE V in the prostate (Tr. 162:25-163:23) and that each of these PDEs (PDE I, PDE IV and PDE V) were functionally relevant (Tr. 166:14-167:7). The '124 patent does not describe any actual tests of any specific inhibitors of any PDE that demonstrated efficacy in treating BPH. And Dr. Uckert testified that he never tested the use of any PDE V inhibitor to treat a man with BPH. (Tr. 185:6-8.) The hard work of actually inventing a method of treating BPH with a selective PDE V

inhibitor that was actually effective in treating BPH was left by these inventors to subsequent researchers. Here, that hard work was done by Lilly in actually inventing an effective treatment using tadalafil for BPH. The owners of the '124 patent are not entitled to reap where their inventors did not sow by taxing that real discovery. Accordingly, for all the above reasons, and as in *Boston Scientific, Fujikawa*, and *Novozymes*, invalidity for non-compliance with the written description requirement follows as a matter of law.

C. The Disclosure of the '124 Patent Does Not Provide an Adequate Written Description for the Billions of Hypothesized Compounds Falling within the Scope of Claim 1

It is unusual to have a claim that fails both the *Boston Scientific* and *Ariad* line of cases. Yet, claim 1 of the '124 patent is exactly such a claim. Here, as mentioned above, the claim recites compounds that are defined solely by their function—an "effective amount" of compounds that are able to selectively inhibit PDE V for the prophylaxis or treatment of BPH. But to support such broad functional language, the '124 patent must (1) adequately describe a sufficient number of representative compounds "to reflect the structural diversity of the claimed genus", *i.e.*, compounds able to selectively inhibit PDE V under the Court's construction; or (2) describe a correlation between the structure of such molecules and the claimed function, such that the reader can envision the members of the genus. *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *Ariad*, 598 F.3d at 1350. As set forth below, the specification of the '124 patent fails both criteria.

1. The Specification of the '124 Patent Does Not Disclose a Representative Number of Species

The '124 patent's disclosure falls far short of describing representative species falling within the full scope of the genus of selective PDE V inhibitors that can be administered in an effective amount for prophylaxis or treatment of BPH for the following reasons.

First, there are ***billions of compounds*** that could possibly selectively inhibit PDE V, and these compounds have widely diverse structures and come from many different chemical classes. Tr. 182:6-184:7; 705:17-706:7; 710:4-16; 737:23-739:8; 739:14-742:22; 753:7-757:7; 757:11-760:18; 1300:4-19; 1301:1-5. The molecules specifically disclosed in the disclosure of the '124 patent do not come close to representing the full structural scope of the incalculable number of compounds from many different classes having widely diverse structures that are encompassed by generic claim 1.

Second, it is ***unpredictable*** which of these billions of possibilities will in fact selectively inhibit PDE V ***and*** be effective in the claimed method for treating or preventing BPH. First, the patent does not identify which of the disclosed compounds selectively inhibit PDE I, PDE IV or PDE V. As to the disclosed classes of compounds, UroPep's expert, Dr. Terrett, testified one would have to make and test them to determine their inhibitory activity. (Tr. 710:17-711:1.) Further, the structure-activity relationship of PDE V inhibitors and their *in vivo* or clinical effects was uncertain and immature before the filing date. A 1993 paper by Takase et al. on the discovery of a novel PDE V inhibitor, noted in relation to "cGMP-PDE inhibitors" (PDE V is specific to cGMP):

> On the other hand, there is little information on the SARs of the cGMP-PDE inhibitors because ***even the most potent inhibitors have very diverse molecular structures, making identification of the most important sites of interaction difficult***. Furthermore, little is known about the *in vivo* actions and clinical effects of selective cGMP-PDE inhibitors.

(PX 242 at p. 3765 (footnotes omitted) (emphasis added)). Subsequent publications (e.g., DX 1368 (Silver) and DX 1377 (Sybertz)), although disclosing more compounds being discovered to inhibit PDE V, only further demonstrated the diversity of their molecular structures.

Between 1993 (when Takase was published) and July 1997 (the filing date of the original application), very little additional insight had been published on the *in vivo* actions or clinical effects of selective PDE V inhibitors. As of the filing date of the '124 patent, only two compounds known to inhibit PDE V (zaprinast and sildenafil) had been clinically evaluated and then only for indications other than BPH. (Tr. 1293:24-1294:12.) Zaprinast was progressed to clinical trials for asthma but abandoned as a potential development candidate. (DX 1377 (Sybertz) at p. 385.) And the efficacy of sildenafil for oral therapy of male ED was still being assessed through clinical trials as of 1996. (PX 183 (Terrett) at pp. 1819-20.

The undisputed trial record also confirms that BPH was a poorly understood and poorly defined disease. For example, Dr. Roehrborn testified that BPH is highly variable and that symptoms wax and wane. (Tr. 525:3-527:4.) Treatment of BPH is very difficult and often complicated by a placebo effect. (Tr. 545:22-547:15; 547:24-548:18.) Not all selective PDE V inhibitors would work when administered to a man to treat his BPH symptoms. (Tr. 517:25-518:7.)

In sum, as admitted by Dr. Terrett, it is ***"impossible to say"*** whether all PDE V inhibitors would work to treat BPH. (Tr. 710:1-3.) In the same vein, Dr. Bell admitted that he did not know whether zaprinast would be effective when administered to a human to treat BPH because "it's never been tested" for the treatment of BPH. (Tr. 338:6-339:9.) This, notwithstanding that zaprinast had been tested at 10 mg for the treatment of asthma before the filing date of the '124 patent. Plainly, therefore, the ability to treat one condition with a selective PDE V inhibitor does not necessarily translate into ability to treat BPH.

Third, UroPep has conceded that Claim 1 would fail for written description if none of the disclosed compounds fall within the scope of Claim 1. (Motions Hearing, Feb. 27, 2017, Tr.

19:3-12.) This is a critical admission, since the '124 patent, on its face, does not identify any compound as expressly being a selective PDE V inhibitor and even more clearly fails to identify any compound as expressly being 20 times more inhibitory for PDE V compared to PDE I-IV in accordance with the Court's claim construction. Within the enormous universe of wildly diverse compounds potentially able to selectively inhibit PDE V, the '124 patent specifically described only ten compounds, and Dr. Bell admitted that the '124 patent does not identify which of those compounds—listed as "a" through "j"—are selective PDE V inhibitors. (Tr. 1306:21-1307:8.)

Moreover, eight of the ten disclosed compounds are expressly ***excluded*** from claim 1 and, therefore, cannot provide the support to meet the written description requirement for what ***is*** claimed. But even if the eight excluded compounds can be considered in the written description analysis, the totality of just ten compounds—none of which is described within the four corners of the specification as a selective inhibitor of PDE V only—is a wholly inadequate disclosure of representative species to reflect the undisputed structural diversity of ***billions of compounds*** from many different classes. Dr. Uckert, the ***only*** inventor who came to trial, did not even know why the list of compounds depicted as "a" through "j" were identified as "preferred selective inhibitors of PDE I, IV and V" in the '124 patent. (Tr. 657:11-15.) Dr. Bell admitted that the patent does not identify which compounds inhibit PDE I, PDE IV or PDE V (Tr. 1306:21-1307:8.) A person of ordinary skill in the art, looking just at the structure of the disclosed compounds and the "four corners" of the specification, could not discern whether the inventors considered any of those compounds as selectively inhibiting PDE V alone (Tr. 737:23-739:8), to say nothing of the needed ability to "visualize or recognize" the other members of the genus of all selective PDE V inhibitors that could be given in an effective amount to prevent or treat BPH. In fact, Dr. Bell admitted that a person of skill in the art would not know whether zaprinast, the

only compound specifically recited in the claimed method (claim 2), would be effective in treating BPH without testing it. (Tr. 338:6-339:9.)

Fourth, the classes of compounds listed as "k" (quinazolines and their trimethoxy derivatives) and "l" (pyrazolopyrimidones) cannot qualify as representative species falling within the scope of the claimed genus of PDE V inhibitors. In fact, the only disclosed compounds within the class of compounds defined by "k" and "l" (compound (g) and compounds (d) and (f)) are ***excluded*** from claim 1. Further, the trial record established that there could be billions of possible compounds falling within these two classes, but not all of them would inhibit PDE V and there would be no way of knowing which ones "selectively" inhibit PDE V without making them and testing them. (Tr. 739:14-742:22.) Dr. Terrett testified that a person of skill in the art could not, for example, identify a compound within the class of quinazolines ("k") that inhibits PDE V without making the compounds and testing them for activity. (Tr. 710:17-711:1.) Dr. Uckert did not know any quinazolines that inhibit PDE V. (Tr. 878:20-21.) He also did not know any pyrazolopyrimidones that inhibit PDE V. (Tr. 879:12-14.) Nor could he identify or distinguish between members of the classes of quinazolines or pyrazolopyrimidones that inhibit PDE I or PDE IV, as opposed to PDE V, or any other PDE. (Tr. 657:6-658:14; Tr. 878:18-879:14.) Considering that the inventor did not know why the disclosed compounds were identified in the patent or whether they inhibited PDE V, one of ordinary skill in the art would at best be equally ignorant. *Ariad*, 598 F.3d at 1356 ("Considering that the inventors of the '516 patent discovered NF-kB, if they did not know the two domains are distinct, one of ordinary skill in the art was at best equally ignorant.").

Fifth, the '124 patent's specification does not describe tadalafil, its chemical structure, its chemical class, or any species structurally similar to tadalafil. It is undisputed that the structure

of tadalafil is not disclosed in the '124 patent. (Tr. 184:22-185:3; 757:13-15.) Nor were there any compounds derived from the "carbazole" class that tadalafil comes from disclosed in the '124 patent. (Tr. 757:16-24.) Nor could a person of ordinary skill in the art have taken any of the disclosed compounds and somehow come up with tadalafil. (Tr. 758:2-23.) The omission of tadalafil or anything like it is a critical omission. Not only is tadalafil not disclosed as a "representative" compound in the '124 patent, but it is an undisclosed compound with unique structure and biological activity that works in the claimed method. (Tr. 962:8-969:18 (Sabo testimony on tadalafil's unique structure and biological activity); *see also* DX 1011 at LILLY-BPH-00782063-64, 72-74, 76-77, 79.) DX 1347 (Dr. Rotella's chapter on "Phosphodiesterases" which was introduced by UroPep), highlights the structural diversity among PDE V inhibitors and how those structural differences contribute to different binding modes and different biological activity. For example, DX 1347 notes that tadalafil is structurally distinct from other approved PDE V inhibitors, which contributes to different binding and different selectivity.

> Tadalafil (Cialis, 6) is a carbazole analog that clearly is structurally distinct from the other approved PDE5 inhibitors. It was developed from a distinct carbazole starting point. The structural difference contributes to a distinct binding mode (see the discussion of the x-ray crystal structures below), which contributes to the substantial difference in PDE6 selectivity between tadalafil and the other approved PDE5 inhibitors.

(DX 1347 at p. 939 (footnotes omitted).) In addition, in DX 1598, a paper authored by Dr. Bell and other Pfizer scientists, Dr. Bell wrote that the "hydrophobic stacking of the quinazoline ring" in the binding modes of sildenafil and another sildenafil-based selective PDE V inhibitor being studied by Pfizer is "key to potency" in those compounds. (DX 1598 at p. 409.) This is another critical structural difference between tadalafil and sildenafil (and other compounds), as Dr. Bell conceded that this particular binding mode that is "key to potency" in sildenafil does not exist in tadalafil because tadalafil does not have a quinazoline ring. (Tr. 1319:11-22.)

Although the '124 patent does not necessarily need to disclose the exact structure of tadalafil, the patent must at least describe some species representative of compounds structurally similar to, and representative of, tadalafil. *AbbVie*, 759 F.3d at 1301 (finding inadequate written description based, in part, on lack of evidence showing that any described antibody was structurally similar to, and thus representative of, the accused product Stelara, or that a person of skill in the art could make predictable changes to the described antibodies to arrive at other types of antibodies such as Stelara). Such a disclosure is absent here.

2. There Is No Disclosed Correlation Between Chemical Structure and the Functional Ability to Selectively Inhibit PDE V and Treat BPH

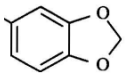
To meet the "structure-function correlation" test under the written description requirement, the '124 patent must establish a correlation between the structure of the claimed compounds and the relevant function set forth in the claim, such that a person of ordinary skill in the art can "visualize or recognize" the members of the claimed genus. *Ariad*, 598 F.3d at 1350. In this case, the relevant function as construed by the Court involves at least three different aspects: (1) inhibition of PDE V; (2) inhibition of PDE V at least 20-fold more than PDEs I to IV as determined by an "IC50" test referenced for other purposes in the patent; and (3) efficacy when administered to a patient in need of treatment for BPH. The text of the '124 patent does not describe, and the trial record contains no competent scientific evidence demonstrating, that the genus of such PDE V inhibitors have structural features that have an established correlation with any of these functions, either individually or together. Rather, the trial record conclusively established that there is ***no correlation*** between chemical structure and the function of selective PDE V inhibition useful in the claimed method.

As noted above, the structures of the full scope of compounds that can selectively inhibit PDE V inhibitors are very diverse. (Tr. 182:6-184:7; 710:4-16; 737:23-739:8; 739:14-742:22;

1300:4-19; 1301:1-5.) The testimony of all the chemistry experts was consistent. Lilly's expert, Dr. Rotella, testified that there is no structure common to the genus of compounds that can selectively inhibit PDE V. (Tr. 753:7-757:7.) Dr. Bell admitted that the structures of compounds that selectively inhibit PDE V are very diverse. (Tr. 1300:4-19; 1301:1-5.) Dr. Terrett also admitted that there is no common structure for PDE V inhibitors. (Tr. 705:17-706:7.) And it was acknowledged in the literature that the structural diversity of molecules inhibiting PDE V made assessment of their structure-activity relationships difficult. (PX 242 at p. 3765.)

UroPep is attempting to cover any compound that can selectively inhibit PDE V used to treat BPH—no matter when discovered and no matter the differences in binding, structure, or chemical and physical properties. (Tr. 184:8-10 ("Q: And you still might discover new PDE V inhibitors that aren't even remotely described in this patent, correct? A. [Uckert] Correct."); *see also* Tr. 1323:11-1324:3 (Dr. Bell testimony that the claimed method would covers newly discovered PDE V inhibitor compounds). That is an improper "attempt to preempt the future before it has arrived." *Ariad*, 598 F.3d at 1353 (quoting *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)). Its legal insufficiency to satisfy the written description requirement is apparent from the four corners of the patent. And there was no substantial evidence at trial demonstrating that the '124 patent's disclosure meets the structure-function correlation test for compliance with the written description requirement.

In an eleventh-hour effort to show some "common structure" that could be tied, no matter how tenuously, to tadalafil, UroPep's counsel led Dr. Bell to a connected ring structure present in a few compounds (Tr. 1259:22-1262:12), which counsel then referred to as the "frog" structure (depicted below).



(Tr. 1260:2-5 ("it looks like a frog with two eyes", referring to the two oxygen atoms depicted by the letter "O").)

The testimony regarding a "frog" structure offered to the jury was a gross and misleading oversimplification of the structure-function issue and is without merit. Nothing in the patent specification describes the "frog" structure as somehow core, critical, or necessary to the claimed method. Nor does the prior art refer to a "frog" structure as alone correlating with selective PDE V inhibition. Indeed, ***only two*** of the ten compounds disclosed in the '124 patent ("d" and "f") have the "frog" as part of much larger molecules (col. 2:29-4:47) and both are ***excluded*** from the '124 patent claims. They cannot, therefore, provide written description support for the compounds falling within the claim. Moreover, the scientific literature discloses compounds identified as PDE V inhibitors that lack this "frog" structure (DX 1377, compounds depicted in Tables VI, VII, VIII, IX, and X), and the "frog" structure is also found in ***PDE IV inhibitors*** (DX 1347, compound 47; at pp. 935-36).

The "frog" structure does not correlate with selective PDE V activity. Indeed, as Dr. Bell admitted, the only "commonality" among compounds that inhibit PDE V is that "they are all inhibitors of PDE V." (Tr. 1279:17-20.) This "frog" simply won't jump to meet the requirement for a common structure correlated to the relevant function.

3. The Disclosure of a Single Useable Compound Would Not Save Claim 1 of the '124 Patent From Invalidity

Contradicting the well-established precedent set forth above, UroPep has continued to assert, relying on *In re Herschler*, 591 F.2d 692 (C.C.P.A. 1979), that the '124 patent satisfies the written description requirement if it describes only *one or more* representative compounds

that selectively inhibit PDE V. That contention was correctly rejected at trial. (Dkt. 330 at pp. 1-2; Tr. 1395:7-22; 1427:10-18.) *Herschler*—a 1979 case that significantly predates the more recent and consistent pronouncements by the Federal Circuit in *Rochester*, *Ariad, Alonso*, and *Boston Scientific*—is not this case.

The patent in *Herschler* claimed a method of using one particular compound (a dimethyl sulfoxide ("DMSO"), "a well-known industrial solvent") to enhance the penetration of an equally well-known class of steroidal agents across human and animal membranes. *Herschler*, 591 F.2d at 695 n.2. In contradistinction to the present case, *Herschler* emphasized the substantial chemical similarity of steroidal agents in holding that the disclosure of a single corticosteroid was sufficient to describe the genus of physiologically active steroids that could be used in practicing the claimed invention:

> The solicitor urges that the class of steroids is so large that a single example in the specification could not describe the varied members with their further varied properties. We disagree with this contention. Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, when considered as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar.

Id. at 701.

The Federal Circuit has consistently confined *Herschler* to that fact pattern. *See Alonso*, 545 F.3d at 1022 n.9 (rejecting patentee's reliance on *Herschler* on the grounds that the *Herschler* court's decision was based on the fact that the class of implicated compounds was "chemically quite similar") (quoting *Herschler*, 592 F.2d at 701); *Boston Scientific*, 647 F.3d at 1363-64 (rejecting patentee's reliance, in part, on *Herschler* for the proposition that when claiming a class of known compounds in a method claim, as opposed to novel compounds, the specification need only be so specific as to lead a person of skill in the art to that class of

compounds). And in *Rochester*, the court rejected essentially the same argument being made by UroPep here, that requiring a disclosure of representative species or common structure-activity is limited to composition of matter claims and does not apply to method claims: "that is a semantic distinction without a difference." 358 F.3d at 926 (quoting district court, *Univ. of Rochester v. G.D. Searle & Co.*, 249 F. Supp. 2d 216, 228 (W.D.N.Y. 2003)).

More directly to the point, any "one compound is enough" reading of *Herschler* was rejected and overruled by the later *en banc* decision from the Federal Circuit in *Ariad*. There, the patentee disclosed at least one inhibitor of NF-kB but was still denied the right to claim methods of using all inhibitors under the written description requirement. *Ariad,* 598 F.3d at 1356. Ariad argued that "because the specification discloses specific example sequences, there is little doubt that the specification adequately described the actual molecules to one of ordinary skill in the art." *Id*. at 1357. Nevertheless, this disclosure was insufficient as a matter of law because there were not actual examples of using decoy molecules to inhibit NF-kB in the claimed method, as the Federal Circuit explained: "Whatever thin thread of support a jury might find in the decoy-molecule hypothetical simply cannot ***bear the weight of the vast scope of these generic claims***." *Id*. at 1358 (emphasis added). Rather, "the specification at best describes decoy molecule structures and hypothesizes with no accompanying description that they could be used to reduce NF-kB activity. ***Yet the asserted claims are far broader.***" *Id*. (emphasis added). The same is true here. Claim 1 of the '124 patent is invalid as a matter of law.

D. Claim 1 Is Also Invalid Because the Written Description Does Not Support Its Negative Limitation

The '124 patent is also invalid under § 112, ¶ 1, because there is no written description or explanation in the specification to support the ***exclusion*** from its scope of eight disclosed and previously claimed compounds, but ***not*** zaprinast. This is "generally inconsistent" with the '124

patent's disclosure that selective inhibitors of PDE V work in the claimed method. *In re Bimeda Research & Development Ltd.*, 724 F.3d 1320, 1323 (Fed. Cir. 2013) (upholding the BPAI's affirmance of an examiner's rejection under § 112 because patent disclosure was "generally inconsistent" with the claimed exclusion). "Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1355 (Fed. Cir. 2015) (quoting *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012). That is not the case here.

The Court rejected Lilly's "negative limitation" argument during trial, concluding that "the reason for the negative limitation is clear on the face of the two patents—the drafters of the '124 patent sought to claim the genus of PDE5 inhibitors, while excluding the compounds that had previously been patented [in the parent '061 patent, Trial Ex. 193]." (Mem. Op., Dkt. 359 at p. 11.) The Court therefore did not give Lilly's requested "negative limitation" instruction. *Id.*

Respectfully, the Court's reasoning is mistaken. Claim 1 of '124 patent did not exclude all the compounds that had previously been patented in the '061 patent or elsewhere. Claim 3 of the '061 patent includes, *inter alia,* zaprinast, which is ***not*** excluded from claim 1 of the '124 patent. *Compare* PX 193, '061 patent, Claim 3(a), col. 8:8-35 *with* PX 1, '124 patent, col. 8:23-40. In fact, dependent claim 2 of the '124 patent expressly claims the "method of claim 1 wherein the compound is [zaprinast]." Thus, the '124 patent's named inventors were ***not*** merely excluding previously claimed compounds or "excising the invention of another, to which they are not entitled." (Dkt. 359 at 12 (quoting *Inphi*, 805 F.3d at 1356).) Even accepting the Court's reasoning that the other compounds were excluded because they were claimed in the '061 patent and sildenafil was separately patented, there is ***no*** explanation for why zaprinast was not excluded since zaprinast was also claimed in the '061 patent. This is precisely the arbitrary

dissection of a unitary invention the written description requirement prohibits. *Inphi*, 805 F.3d at 1356-57 (citing *Bimeda*, 724 F.3d at 1322). JMOL should be entered in Lilly's favor on its "negative limitation" defense. At a minimum, a new trial should be granted because the Court erred in refusing to give the requested jury instruction regarding the negative claim limitation.

V. CLAIM 1 OF THE '124 PATENT IS INVALID AS A MATTER OF LAW FOR LACK OF ENABLEMENT

A. The Specification of a Patent Must Teach Those Skilled in The Art How to Make and Use the Full Scope of The Claimed Invention Without Undue Experimentation

Separate from the written description requirement is the "enablement" requirement of 35 U.S.C. § 112, ¶ 1 (a patent's specification must describe the invention and "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same").

> Enabling the ***full scope*** of each claim is part of the *quid pro quo* of the patent bargain. A patentee who chooses broad claim language must make sure the broad claims are fully enabled. The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.

Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir. 2008) (quotations and citations omitted) (emphasis added). Whether the enablement requirement has been satisfied is a question of law based upon underlying facts, and is determined as of the patent's effective filing date. *Id*.

While some experimentation is permitted under the patent law, the amount of experimentation must not be "undue." *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013) (citing *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1380-81 (Fed. Cir. 2012). Further, "[c]laims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice *their full scope*." *Id*.; *see also ALZA Corp. v. Andrx*

Pharms., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010) ("To be enabling, the specification of a patent must teach those skilled in the art how to make and use ***the full scope*** of the claimed invention without 'undue experimentation.'") (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2 1557, 1561 (Fed. Cir. 1993) (emphasis added). In determining whether experimentation is "undue," the following factors may be considered: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *ALZA*, 603 F.3d at 940 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

The Federal Circuit's decision in *Wyeth* is especially instructive here. In that case, the Federal Circuit found on summary judgment that a method of treatment claim to the use of functionally described analogs to a structurally claimed compound was not enabled as a matter of law. 720 F.3d at 1386 The patent claims in *Wyeth* recited a method of treating or preventing "restenosis in a mammal . . . which comprises administering an antirestonosis effective amount of rapamycin to said mammal." *Id.* at 1382. Rapamycin was acknowledged to refer to a class of compounds. However, the parties agreed that even though the patent referred to "rapamycin," the specification disclosed only one rapamycin species called sirolimus having a specific structure. *Id.* As urged by the patentee, the district court broadly construed the claims to encompass any structural analog of sirolimus that exhibits immunosuppressive and antirestonosis effects. *Id.* at 1384. In view of this broad construction, the district court held that practicing the full scope of the claims required excessive—and thus undue—experimentation. *Id.* Although the specification described assays to ascertain whether a potential rapamycin compound exhibits the recited

functional effects, the only species disclosed was sirolimus. *Id.* Further to its finding of nonenablement, the district court relied on the unpredictability of the chemical arts, the complexity of the invention, and the limited knowledge of treatment of restenosis using sirolimus at the time of the invention. *Id.*

The Federal Circuit accepted as true Wyeth's claims about the state of the art, that potential rapamycin compounds would be limited to molecular weights below 1,200 Daltons in order to be permeable across cell membranes, and that a person of skill in the art could routinely use the assays described in the specification to determine immunosuppressive and antirestonosis effects in candidate compounds. *Id.* Nonetheless, even accepting those assertions, the Federal Circuit found nonenablement as a matter of law for several reasons. First, the Court found the scope of the claims is "broad." *Id.* at 1385. The claimed invention was described as "a new method of use of a known compound (sirolimus) *and* any other compounds that meet the construction's structural and functional requirements." *Id.* (court's emphasis). Second, the specification's guidance was "limited to disclosures of the immunosuppressive and antirestenotic properties of sirolimus and assays to screen for those properties." *Id.* Third, even limited by molecular weight, there were still at least tens of thousands of candidate compounds. *Id.* Fourth, the specification was silent about how to structurally modify sirolimus to come up with new compounds—let alone in a way that would preserve the recited utility. *Id.*

Therefore, the *Wyeth* court found that "it would be necessary to first synthesize and then screen ***each*** candidate compound using the assays disclosed in the specification to determine whether it has immunosuppressive and antirestonotic effects." *Id.* (court's emphasis). Further, "[t]here is no evidence in the record that any particular substitutions outside the macrocyclic ring are preferable." *Id.* And a Wyeth scientist confirmed that the art was unpredictable and that one

would need to assay each candidate compound, testifying that "until you test [compounds], you really can't tell whether they work or not [*i.e.,* have antirestonotic effects]." *Id.* (court's bracketed words). "In sum, there is no genuine dispute that practicing the full scope of the claims would require synthesizing and screening ***each*** of at least tens of thousands of compounds"—which the court found was undue experimentation, even if routine. *Id.* (court's emphasis).

B. As in *Wyeth*, The Full Scope of Claim 1 Of The '124 Patent Cannot, As A Matter of Law, Be Practiced Without Undue Experimentation

Lilly submits that *Wyeth* is controlling in this strikingly similar fact pattern. As in *Wyeth*, the specification of the '124 patent discloses only "a starting point for further iterative research in an unpredictable and poorly understood field." 720 F.3d at 1386. The '124 patent lacks important guidance and fundamental criteria needed to enable a person of skill in the art to practice the full scope of the claimed method without undue experimentation—much of which is the same missing information that is fatal to compliance with the written description requirement outlined in § IV., *supra*. Indeed, the cases acknowledge that for this reason a patent's compliance with the written description and enablement requirements will often stand or fall together. *See, e.g.*, *LizardTech, Inc. v. Earth Res. Mapping, Inc*., 424 F.3d 1336, 1345 (Fed. Cir. 2005).

As previously noted, inventions involving the biological and chemical arts are more unpredictable than the mechanical or electrical arts where a single embodiment may provide broad enablement. *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). The nature of the invention relates to the use of an unknown but enormous and structurally diverse genus of potential compounds, with widely varying chemical and physical properties, to treat a disease in a person (BPH) that was and is highly variable, poorly understood and poorly defined. (Tr. 525:9-527:4.) Treatment of BPH symptoms is complicated and difficult. (Tr. 545:22-547:15; 547:24-548:18.) The '124 patent provides no guidance as to treatment of BPH, how to evaluate treatment of BPH,

how to measure improvement of BPH symptoms, how to account for the "waxing and waning" of symptoms, or what constitutes "treatment" of the condition. (Tr. 545:5-21; 547:16-19.)

In addition, as discussed *supra* at § IV, there was very little known prior to the filing date of the '124 patent about even the *in vitro* (in the lab) structure-activity relationships of PDE V inhibitors. Even less was known about the structure-function relationships of PDE V inhibitors *in vivo* (in a person). As noted above, as of 1997, only two PDE V inhibitors (sildenafil and zaprinast) had been clinically studied, both for conditions other than BPH, and none had been approved by the FDA.

In order to meet the enablement requirement, the specification of the '124 patent must disclose to a person of skill in the art how to practice the full scope of the claim, i.e., by at least identifying the genus of compounds able to selectively inhibit PDE V and be administered in an effective amount in the claimed method to treat BPH. At the outset, the skilled artisan would first need synthesize many candidate compounds just to identify those that selectively inhibit PDE V. As previously noted, the number of compounds able to selectively inhibit PDE V is unknowable, but enormous, and very likely within the range of billions. (Tr. 182:6-184:10; 710:4-711:1; 742:2-22; 743:4-22.) The quantity of experimentation just to accomplish a research project directed at identifying selective PDE V inhibitors is exceedingly high, considering that the specification of the '124 patent fails to describe any specific compound as a selective PDE V inhibitor and fails to disclose a representative number of claimed species or a correlation between chemical structure and selective PDE V inhibition such that the skilled artisan could visualize and recognize the members of the claimed genus.

Once a person of skill in the art had synthesized this unknowable but large number of compounds, they would then have to test them to determine if they were sufficiently potent

inhibitors of PDE V—but, as discussed below, even potency does not predict efficacy in a person. Thus, information regarding each compound's functional properties (bioavailability, absorption, metabolism, etc.) would have be determined to ascertain whether that compound would ever reach the target cell to have any effect—all of which would be highly unpredictable. (Tr. 523:23-528:9.) The skilled artisan would also have to conduct additional tests to determine selectivity for PDE V compared to PDE I, PDE II, PDE III and PDE IV.

The testimony of all the experts (Lilly's and UroPep's) demonstrates that screening and synthesizing candidate compounds would, itself, require complicated and lengthy experiments in synthetic organic chemistry, including assays of compounds potentially numbering in the billions—and that would only be the starting point to trying to identify which compounds out of these billions could be given in an effective amount to a person to treat BPH. (Tr. 523:23-528:9; 528:23-532:17; 532:18-533:16; 534:7-11; 685:14-691:22; 710:1-3; 710:23-711:1; 720:14-721:6; 728:22-732:7; 761:5-762:14; 773:25-774:18.) *See Wyeth*, 720 F.3d at 1386 ("Synthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry. Even putting the challenges of synthesis aside, one of ordinary skill would need to assay each of at least tens of thousands of candidates."). And it would be wholly unpredictable which of these many candidate compounds would also work to treat BPH. (Tr. 532:8-17; 535:7-19; 543:2-12; 546:4-547:15; 710:1-3; 764:3-766:23; 774:19-775:22.)

The '124 patent is even further removed from an enabling disclosure than the patents in *Wyeth*. The claim in *Wyeth* at least recited some structure, an analog of sirolimus. Here, claim 1 of the '124 patent recites no structure but describes the compounds merely by function and desired effect in a method of treating a disease. In *Wyeth*, the candidate compounds numbered at

least in the tens of thousands; here, the evidence is that the number of candidate compounds is at least that but likely many times more (***billions***). (Tr. 182:6-184:10; 710:4-711:1; 742:2-22; 743:4-22.) In *Wyeth*, the evidence was that it would take technicians "weeks" to complete these assays. This trial record here showed it would take much longer, likely many years. (Tr. 542:9-544:2; 774:19-776:24.) Indeed, it took Lilly about ten years of studies, involving dozens of scientists, physicians, and researchers, to prove that ***just one compound*** (tadalafil) could be administered in an effective amount for the treatment of signs and symptoms of BPH. (Tr. 915:5-939:4 (Viktrup testimony on Lilly's tadalafil studies); Tr.1003:5-1004:13 (Sabo testimony on Lilly's tadalafil studies); *see* Lilly tadalafil study exhibits (DX 1095; DX 1096; DX 1097; DX 1098; DX 1100; DX 1102).) And it took Bristol-Myers Squibb about four years to screen selective PDE V inhibitors for Erectile Dysfunction. (Tr. 721:17-724:22.)

There is no guidance in the specification of the '124 patent as to the chemical structure or functional characteristics of candidate compounds that would enable each compound to work in the claimed method to treat BPH. As in *Wyeth*, the greatly variable structures of known PDE V inhibitors, and that art-recognized difficulty in identifying structure-function relationships in that class noted previously (PX 242 at 3765), provide no guidance regarding additional structural modifications likely to result in workable inhibitors.

Moreover, simply identifying compounds that selectively inhibit PDE V is not enough. As in *Wyeth*, the compounds are claimed for use in a method of treatment. Both the patent claim in *Wyeth* and claim 1 of the '124 patent require the administration of an "effective amount" of the claimed functionally described compounds—in a "mammal" in *Wyeth* and in a "person" in the '124 patent claim. As in *Wyeth*, the specification of the '124 patent offers no guidance or predictions about the full scope of the claimed genus of compounds to achieve efficacy in the

claimed therapeutic treatment. In fact, the '124 patent's specification provides no information about any effects observed with any particular compound, whereas in *Wyeth*, the specification at least provided information regarding immunosuppressive and antirestonotic effects observed with sirolimus, a specific compound within the scope of the claims. The '124 patent provides no differentiation between inhibiting PDE I, PDE IV or PDE V in the context of relaxing smooth muscle generally and certainly not in the specific context of treating BPH. The patent does not even say whether the disclosed compounds inhibit PDE I, PDE IV, or PDE V, or a combination of those PDEs.

Nor does the patent provide information or guidance about the physical or biological activity of any compound that might be used in the claimed method. Then, those compounds would have to be tested to determine which ones could be administered in amounts effective actually to treat BPH. It bears repeating the admission of Dr. Terrett: It would be "impossible to say" whether all compounds that inhibit PDE V would work to treat BPH. (Tr. 710:1-3.) And the '124 patent provides no disclosure that would enable a person of skill in the art to reasonably identify or predict which of the billions of potential compounds could be administered in an effective amount to treat BPH. In fact, the only experiment reported in the '124 patent provides no guidance regarding identification of a selective PDE V inhibitor that is actually effective to treat BPH. The description of the *in vitro* organ bath test provided in the patent does not state what compounds were tested, at what concentration they were tested, what the relaxing effect was, or which of the inhibitors of PDE I, PDE IV or PDE V had the strongest relaxing effect. (Tr. 518:14-519:11; 528:23-531:4.)

As noted, potency is merely a starting point in trying to determine whether a candidate compound will have efficacy in a human—but the patent does not even provide information

about "potency" of any inhibitor compound. There is nothing in the specification about what concentration must be present for the compound to be effective *in vitro* or *in vivo*, whether there is a minimum potency, or whether there is a recommended range of potency. While the claim as construed by the Court requires "selectivity," "selectivity" and "potency" are not the same thing. There is also *in vitro* potency (measured by IC_{50}) as well as *in vivo* potency (which assesses the drug concentration at which the desired pharmacologic effect is observed). Both are important to assess undisclosed compounds embodied by the full scope of the claim; neither are disclosed in the patent. Moreover, selectivity assesses whether a compound preferentially inhibits one form of PDE over others without regard to the drug concentration needed to attain that effect in a body. Thus, a PDE V inhibitor could be exquisitely selective but of such low potency that its effects are observed only at unusably high concentrations. Indeed, that is precisely UroPep's argument relating to Horny Goat Weed (although Horny Goat Weed is sufficiently enabled to anticipate, *See* § VIII., *infra*.). Thus, while Dr. Bell conceded that some minimal potency is essential for effective treatment of BPH (Tr. 334:6-19), he also had to concede that the '124 patent is silent regarding what that potency is. (Tr.334:20-335:24.) And, notably, the patent provides no information about the potency or selectivity of the disclosed compounds. (Tr. 541:9-542:8.)

The two "examples" in the '124 patent also do not help at all. The testimony by both Drs. Roehrborn and Rotella was uncontroverted. Those examples are confused, nonsensical and almost certainly non-workable to demonstrate enablement of an effective amount of a selective PDE V inhibitor to treat BPH. (Tr. 537:10-540:13; 772:20-773:24.) No UroPep witness testified that following the examples of the '124 patent would result in the administration of an "effective amount" of a PDE V inhibitor for prophylaxis or treatment of BPH.

Further exemplifying the undue experimentation resulting from the paucity of disclosure in the '124 patent is Dr. Bell's admissions regarding his own work at Pfizer in which he, along with a team of Pfizer scientists, spent some six or seven years screening hundreds of thousands of compounds to try to identify selective and potent PDE V inhibitors as clinical candidates. But unlike a researcher who would have to use the '124 patent's disclosure as a starting point, Dr. Bell and his colleagues actually started with a set of "key criteria" that "were designed to give confidence that any new emerging chemical lead series would have the capability of providing a clinical candidate with the desired highly PDE5 selective and once daily dosing profile." (Tr. 1309:13-1314:9; DX 1598 at p. 406.) These criteria included potency, physicochemistry (e.g., molecular weight), and absorption/metabolism that was indicative of good membrane permeability and predicted human half-life. (DX 1598 at p. 406.) The criteria that Dr. Bell and his Pfizer colleagues relied on—which is also the necessary criteria that Drs. Roehrborn and Rotella identified—is noticeably absent from the disclosure of the '124 patent as Dr. Bell admitted. (Tr. 1312:22-1314:4.) The importance of such criteria to the level of experimentation is highlighted by the fact that even starting with much more in the way of key criteria for identification of a useable drug candidate than is provided in the '124 patent, Dr. Bell and his Pfizer scientists, after six years, identified only a handful of potential clinical PDE V candidates out of 500,000 compounds. (Tr. 1314:19-1315:25.) As Dr. Bell explained, "[t]hat's how drug discovery works" (Tr. 1315:9); it is "unpredictable." (Tr. 1316:10-14.)

In view of the breadth of the claims, the quantity of experimentation needed to enable their full scope is excessive and undue. (Tr. 542:9-544:2; 770:2-771:18; 774:19-776:15.) As in *Wyeth*—and as demonstrated by real world studies by Lilly, Bristol Myers Squibb, and Pfizer—the "need to engage in a systematic screening process" for each of the many candidate

compounds to first, identify which ones selectively inhibit PDE V and then, which ones can be given to a person, in an "effective amount," to treat a disease like BPH is "excessive experimentation." *Wyeth*, 720 F.3d at 1386. As noted in *Ariad* and above in the context of the written description requirement, the alleged invention of the '124 patent is at best an unpatentable research plan, leaving to others the hard work of actually making the invention. Such a disclosure complies with neither the written description nor the enablement requirement.

C. The '124 Patent Specification Does Not Enable Identification of PDE V Inhibitors 20 Times More Selective for PDE V Than PDE I-IV

On the critical issue of the required PDE V "selectivity," UroPep alleged that the '124 patent cited three articles describing how to make that determination. Two of them, Galvan and Nicholson, were proven at trial not to report determination of PDE V selectivity or even test for PDE V. The sole remaining publication, a 1995 publication on which the named inventors are authors (DX 1390, "Truss"), was proven incapable of assessing the PDE V selectivity claimed.

UroPep alleged that Truss discloses a "peak fraction" method to identify compounds that are 20-times more selective for PDE V than PDE I through IV. However, as the uncontroverted testimony by Dr. Beavo demonstrates, this peak fraction test is by no means "routine" or reliable. Indeed, its use by the inventors of the '124 patent did not even enable them to identify zaprinast as a selective PDE V inhibitor (even though the inventors claimed zaprinast as such in claim 2). No other method for making this critical determination is disclosed.

The selectivity test described in Truss was a "peak fraction" assay that used "pooled" fractions that contained many different proteins and PDEs. As such, Dr. Beavo testified that it could neither (1) identify PDE V (as distinct from some other PDE). nor (2) evaluate a compound's selectivity for PDE V as compared to other PDEs. (Tr. 683:7-690:17.) This fundamental defect in the '124 patent's disclosure is reflected in the Truss's discussion of

zaprinast—the only compound specifically claimed in the '124 patent as a selective PDE V inhibitor (unasserted dependent claim 2).

Table II of Truss reports zaprinast's inhibitory effects on various peak fractions, including three peak fractions that allegedly contained PDE V, specifically, fractions "A1, G1 and G2." (DX 1390, p. 898.) While zaprinast inhibited peak fraction A1, that fraction was described by Truss as "hydrolyzing ***cAMP***." (Tr. 685:14-686:12.) Fraction A1 could not, therefore, have been specifically PDE V because PDE V specifically hydrolyzes only ***cGMP***. (Tr. 686:13-687:9.) That inconsistency, as well as the fact that the IC_{50} value given by Truss for zaprinast was substantially different from IC_{50} values obtained by other tests (compare, e.g., PX 183), led Dr. Beavo to "doubt whether this [A1] fraction at least is PDE V. At the very least, it contained a lot of other PDEs." (Tr. 686:13-687:9.) The other reported PDE V peak fractions (G1 and G2) in the Truss experiment showed *no* inhibitory effect for zaprinast, which again demonstrates that these fractions were not pure PDE V (assuming they contained PDE V at all). (Tr. 688:20-24.) As Dr. Beavo testified, the methods described in the 1995 Truss paper for determining selectivity would not have identified a selective PDE V inhibitor. Rather, they would have given the "wrong answer," would have been "of really no help," and thus would have led a researcher away from identifying selective PDE V inhibitors. (Tr. 690:7-17.) The results reported in Truss are inconsistent with the identification of a selective PDE V inhibitor under the Court's claim construction that would be "suitable" for use in the claimed invention.

Remarkably, no UroPep witness rebutted Dr. Beavo's testimony or testified that the methods used in the 1995 Truss paper and relied upon by the '124 patent would have been usable by a person of ordinary skill in the art to identify selective PDE V inhibitors. Rather, UroPep suggested that the person of ordinary skill in the art would have effectively disregarded the '124

patent's teachings and used different peak fraction tests, such as those used by Pfizer. Again, however, Dr. Beavo testified without contradiction that these other tests, performed on different tissue, would have generated differing results, with no guidance in the '124 patent as to which results should be relied upon. (Tr. 696:8-697:5; 700:23-701:8; 701:13-702:18.) Indeed, UroPep's invitation to go outside the '124 patent's disclosure and assumption that a person of ordinary skill in the art would have developed their own, different tests to try to measure a compound's selectivity for PDE V is itself a concession that the '124 patent is, at best, a very basic research proposal inviting someone else to perform a lengthy, complex research project actually to make the invention. As the Federal Circuit has observed, "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1366.

D. Dr. Bell's Conclusory Characterization of The Experimentation As "Routine" Is Not Substantial Evidence

Dr. Bell's attempt to rebut this evidence by summarily stating that such experimentation is "routine" is not only too conclusory to be credited (Tr. 1295:23-1296:23), *see Sitrick*, 516 F.3d at 1001 (rejecting expert's conclusory assertions on enablement without some support in the patent's disclosure), but, more importantly, was contradicted by his testimony regarding his own work to synthesize and develop selective PDE V inhibitors. (Tr. 1309:13-1318:11; DX 1598.) Dr. Bell himself found that identification of selective, sufficiently potent PDE V inhibitors to treat any disease, including BPH, is ***unpredictable.*** **(**Tr. Tr. 1316:10-14.) Unpredictability, however, is not a license to disclose little and invite those attempting to practice the full scope of the claims to cast about blindly with no more guidance than the original inventor. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). The fact that those in the art

routinely conduct some experimentation does not mean that ***all*** experimentation is thus "routine" within the patent law.

Wyeth is again instructive on this point. Even if all these experiments to synthesize and screen candidate compounds would be "routine," the Federal Circuit in *Wyeth* emphasized that "routine experimentation is 'not without bounds.'" *Wyeth*, 720 F.3d at 1386 (quoting *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013)). In *Wyeth*, the specification disclosed assays that could be used in experimentation (which the court accepted as "routine") to determine candidate compounds that have the desired effect. Nonetheless, the court held that the need to engage in a systemic screening process for at least tens of thousands of candidate compounds to determine which ones have the desired effect to be used in a method claim to treat or prevent restenosis is undue experimentation. *Id.* at 1385-86.

Simply providing an assay is no substitute for actually making the invention that is claimed. That is particularly true here, where the assays described in the '124 patent to assess PDE V selectivity either did not even test for PDE V inhibition or were proven without contradiction to be incapable of doing so. (*See* § V.C., *supra*.)

E. The Void in the Enabling Disclosure of the '124 Patent Cannot Be Filled by Reference to Ordinary Skill in the Art

UroPep's reliance on the prior art and the knowledge of its own expert and his cohorts at Pfizer cannot be used to substitute for an enabling disclosure. *Genentech*, 108 F.3d at 1365-66. Although "a specification need not disclose what is well known in the art," that general statement is "merely a rule of supplementation, not a substitute for a basic enabling disclosure." *Id.* at 1366.

> It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of

> any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure relating to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention to constitute an adequate enablement.

Id.

As in *Genentech*, UroPep is attempting to bootstrap a vague statement of a problem—how to relax prostatic smooth muscle by inhibiting PDE I, PDE IV, and PDE V—into an enabling disclosure sufficient to dominate Lilly's actual solution of the problem. This it cannot do. "Tossing out the mere germ of an idea does not constitute enabling disclosure." *Id.* It is not sufficient for the specification to provide merely "a starting point, a direction for further research"; rather, the specification must provide "reasonable detail" sufficient to enable a person of ordinary skill in the art to make or use the invention across its full scope. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007). The '124 patent at best provides merely an invitation to experiment—to conduct tests to find selective PDE V inhibitors and then more tests to determine which selective PDE V inhibitors can be given in an effective amount to treat BPH. There was not substantial evidence to support the jury finding of enablement and, therefore, JMOL is warranted.

VI. JUDGMENT AS A MATTER OF LAW SHOULD BE GRANTED THAT THE CLAIM 1 IS INDEFINITE IN VIEW OF THE TRIAL TESTIMONY

The Court previously denied Lilly's motion for summary judgment that claim 1—in particular, the requirement that the claimed "inhibitor of phosphodiesterase (PDE) V" be at least 20 times more effective against PDE V than PDEs I-IV—was indefinite. (Mem. Op. & Order, Dkt. 234 at pp. 34-47.) In finding that the claim term was not indefinite, the Court relied on the "general procedure" in reference to the Truss 1995 paper (DX 1390) as well as two other papers

disclosed in the '124 patent. (Dkt. 234 at pp. 36-37.) Based on those papers, "the Court concludes that there is sufficient guidance in the specification to teach a person of skill in the art to perform the tests necessary to determine the IC_{50} ratios required by the claims." (*Id.*)

As discussed above, the uncontroverted testimony by Dr. Beavo establishes that neither the Truss 1995 paper nor the other papers referenced in the patent provide sufficient guidance to a person of ordinary skill in the art. (Tr. 658:17-691:22.) Dr. Beavo testified that the UroPep authors in the Truss paper did not show they had found PDE V in the tissue or that zaprinast (a specifically claimed compound) inhibited PDE V in the manner required by the Court's claim construction. (*See id.*; *see, esp.* Tr. 689:17-690:6.) Consequently, following the instructions given in the Truss paper or the other two papers referenced in the '124 patent "would be of really no help. In fact, it would probably give . . . the wrong answer." (Tr. 690:7-17; *see also* Tr. 691:2-22 (testifying that the Galvan and Nicholson papers are also unhelpful because those papers do not identify how to find PDE V in any tissues and do not even assay for it).) To the extent the peak fraction test disclosed in the patent could be modified as performed by Pfizer, Dr. Beavo's unrebutted testimony that the many variations of looking at peak fractions, performed on different tissues, would have generated differing results. (Tr. 691:2-22; 701:4-702:18.)

Dr. Bell admitted that "there are significant questions raised about the porcine detrusor model in Truss given that the authors report a fraction of cAMP hydrolyzing PDE containing PDE V." (Tr. 1308:14-19.) It is undisputed, as admitted by Dr. Bell, that "the one thing that PDE5 doesn't do is elevate cyclic AMP. It only keeps levels of cyclic GMP up." (Tr. 1289:16-18.) Thus, consistent with Dr. Beavo's testimony, the Truss paper's disclosure of zaprinast as elevating cAMP leads one in the wrong direction., away from inhibiting PDE V. (*See* Tr. 1289:19-1290:5 (Dr. Bell testimony that the disclosure of cAMP-specific inhibitors to relax

smooth muscle in DX 1273 would lead one away from inhibiting PDE V). As discussed above, UroPep's only response was that the patent's reference to the Truss paper at least would signal to persons of skill in the art to use a different peak fraction method, such as that used by Pfizer scientists. (E.g., Tr. 702:5-703:4.) But those methods were not disclosed in the patent.

An important basis for the Court's finding that the claim term was not indefinite was effectively shattered at trial by Dr. Beavo's uncontroverted testimony. Respectfully, based on the evidence elicited at trial by both Dr. Beavo and Dr. Bell and in view of the controlling Federal Circuit law and undisputed facts presented to the Court during summary judgment, Lilly submits that the Court should reconsider its prior summary judgment ruling and enter judgment that claim 1 of the '124 patent is indefinite as a matter of law.

VII. CLAIM 1 OF THE '124 PATENT IS INVALID FOR OBVIOUSNESS UNDER 35 U.S.C. § 103

Lilly's contentions regarding obviousness as a matter of law were set forth in its pre-verdict JMOL motions and are incorporated herein by reference. As discussed above, controlling Federal Circuit law mandates that the disclosure in the '124 patent of a research plan, the "mere germ of an idea," is insufficient as a matter of law to demonstrate an adequate written description or enablement for the invention claimed in claim 1. But if that is enough to satisfy written description and enablement for this claimed invention, then the prior art already taught as much. Consequently, under that circumstance, a conclusion of invalidity for obviousness is compelled.

More specifically, the '124 patent makes the following statements, each of which was admitted to be well known in the art before the filing date of the '124 patent:

- BPH is the growth of the prostate and may result in severe difficulties in micturition (urination). ('124 pat., col. 1:9-14.)

- Because smooth muscle cells account for a large portion of the total prostatic tissue (at least 35%), the '124 patent states that "a distinct improvement of miction [sic.] can be achieved by means of a pharmacologically induced relaxation of these muscle cells." (*Id.*, col. 1:20-24.)
- Compounds known as alpha-receptor blockers (or alpha blockers) were known in the art as of July 1997 that pharmacologically induced relaxation of prostatic smooth muscle to treat BPH. (*Id.*, col. 1:24-26.)
- Increasing the levels of cAMP and cGMP in smooth muscle cell results in the relaxation of that smooth muscle. (*Id.*, col. 1:39-42.)
- cAMP and cGMP are hydrolyzed by PDEs and that "[i]nhibitors of the PDEs in turn reduce the digestion of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell." (*Id.*, col. 1:42-52 (this "mechanism of action" has been described in the prior art).)

Based on these statements in the '124 patent, the jury was legally required to find that a person of ordinary skill in the art as of July 1997 would know: (a) urinary symptoms associated with BPH could be improved by relaxing smooth muscle in the prostate; (b) alpha blockers treated BPH by relaxing prostatic smooth muscle, and (c) inhibition of PDEs reduce the digestion of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell. "Admissions in the specification regarding the prior art binding on the patentee for purposes of a later inquiry into obviousness." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007); *see also Sjolund v. Musland*, 847 F.2d 1573, 1577-79 (Fed. Cir. 1988) (patent specification admitted that certain matter was prior art, and thus "the jury was not free to disregard [that matter]" and "must have

accepted [it] as prior art, as a matter of law"). Moreover, these admissions in the '124 patent were separately established at trial. Dr. Roehrborn's testimony regarding the pre-1997 use of alpha blockers to treat BPH by relaxing prostatic smooth muscle was uncontroverted. (Tr. 481:12-20; see also DX 1296.) Dr. Uckert admitted that it was already known in the art that inhibiting PDEs increases cAMP and cGMP resulting in smooth muscle relaxation. (Tr. 174:9-175:6.)

The jury was, therefore, legally required to find that a person of skill in the art would believe that relaxing prostatic smooth muscle could treat BPH and that inhibition of PDEs that would increase levels of cAMP or cGMP resulting in smooth muscle relaxation. Moreover, Burnett (DX 1245) established that the NO-cGMP pathway is functional in the prostate and contributes to the smooth muscle relaxation mechanism already known to be relevant to treating BPH. (Tr. 499:24-506:3; *see generally* Tr. 494:23-516:13; *see also* DX 1226, DX 1368, DX 1377, DX 1240.)

UroPep's only response to the testimony establishing the relevance of the NO-cGMP pathway to cause smooth muscle relaxation to treat BPH was to point out that "PDE V" is not mentioned in Burnett (DX 1245). Yet, as noted in the foregoing written description discussion (§ IV.B., *supra*), UroPep's original 1997 patent application likewise did not specifically describe the use of just a selective PDE V inhibitor to treat just BPH. It merely taught that "PDE I, IV and V" were of "particular importance" in prostate muscle and did not specifically call out selective PDE V inhibition as a basis for treating just BPH.

In this regard, the original text leading to the '124 patent similarly did not recognize any distinction between treating BPH and treating "impotence." The testimony was uncontroverted that the PDE V inhibitor sildenafil (Viagra®) had been given in an effective amount to a human

to relax smooth muscle in the penis to treat impotence, or ED. (Tr. 508:12-512:14; 515:19-516:7; DX 1226; DX 1240.) To the extent that the alleged invention of claim 1 is based on the recognition that the PDE inhibition required for relaxation of prostrate muscle was different from the PDE inhibition required for treating impotence, that distinction is also not recognized or discussed in the '124 patent.

In summary, the prior art already taught as much of claim 1 of the '124 patent as was initially described in the original application that UroPep asserts supports this later claim. That original disclosure did not recognize any special role for PDE V alone in treating just BPH. If such a limited disclosure is a sufficient written description and enabling disclosure for that later claimed invention, then the purported invention is obvious as a matter of law in view of essentially the same disclosure in the prior art.

VIII. CLAIM 1 IS ANTICIPATED

A. Legal Standards for Anticipation

A reference is anticipatory under 35 U.S.C. § 102(b) if "the prior art reference . . . disclose[s] each and every feature of the claimed invention, either explicitly or inherently." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) (citation omitted). Even if a prior art reference does not explicitly disclose all features of the claimed invention, a reference may inherently do so. *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). "Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Id.* Such inherent anticipation does not require recognition in the prior art; nor does inherent anticipation require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *Id.* "An inherent structure, composition,

or function is not necessarily known." *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999). "[R]ecognition by a person of ordinary skill in the art before the critical date [of the patent] is not required to show anticipation by inherency." *Schering*, 339 F.3d at 1377.

B. Substantial Evidence Does Not Support the Jury's Verdict That Claim 1 Of The '124 Patent Is Not Anticipated By Cheung

1. Cheung Is a Printed Publication

The evidence that Cheung (DX 1551) is a printed publication under 35 U.S.C. § 102(b) was uncontroverted at trial. To qualify as a printed publication under § 102(b), "a reference must have been sufficiently accessible to the public interested in the art." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (internal quotations omitted). Mr. LaForgia testified that: Cheung was advertised in catalogs that were mailed by Dr. Cheung to interested persons several times every year (Tr. 885:17-886:10; 888:4-21; 889:9-18); Cheung was available at the library for the American College of Traditional Chinese Medicine (Tr. 890:1-9); he had personally seen Cheung in the library of the American College of Traditional Chinese Medicine prior to the filing date of the '124 patent (Tr. 891:2-20); and he wrote a review for Cheung because he would benefit from the publicity that he would get from the monograph being distributed to a large number of his colleagues (Tr. 892:14-21). UroPep did not present any evidence to rebut Mr. LaForgia's testimony. Thus, there is no evidence on which the jury could have found that Cheung is not a printed publication that was available before the filing date of the '124 patent.

2. Cheung Discloses Each and Every Element of Claim 1, Either Explicitly or Inherently

The trial record demonstrates that Cheung, published in November 1994, disclosed the use of a selective PDE V inhibitor (*Herba Epimedii*, or Horny Goat Weed, which contains

icariin) that was given to patients suffering from BPH. Tr. 548:20:559:12; 573:3-5; 625:15-23. In addition, given that 94% of those patients reported improvement of symptoms, a reasonable jury could not have concluded that this was not an effective amount of a selective PDE V inhibitor. Anticipation was established, as reflected in the following claim chart.

Claim 1 Limitation	**Where Disclosed in Cheung**
method for prophylaxis or treatment of benign prostatic hyperplasia	Cheung discloses a method of prophylaxis or treatment of BPH. DX 1551, cover page, pp. 1, 80-81; Tr. 549:3-551:20.
administering to a person in need thereof	Cheung discloses the administration of 15 grams per day of Horny Goat Weed (*Herba Epimedii*) to patients with BPH or prostatism (urinary symptoms associated with an enlarged prostate). Tr. 551:3-20; 552:22-553:1; 554:2-20; 558:21-559:9. DX 1551, pp. 80-81. Prostate Hypertrophy – Clinical Observation – 34 Cases. Seventeen cases had ultrasound examination. Dosing: one pack a day for 6-7 weeks. Each pack contained 15 gms of Hb. Epimedii.
an effective amount of an inhibitor of phosphodiesterase (PDE) V	Cheung teaches that the administered composition was in an "effective amount", as the results of treatment over a 6-7 week period showed an improvement in urinary dysfunction within 3-4 weeks and an effective treatment rate of 94%. Tr. 552:22-553:1; 554:2-20; 557:3-25; 558:21-559:9. The measurement of efficacy based on symptom improvement is the same as how the efficacy of Cialis is evaluated. Tr. 557:3-25 DX 1551, pp. 80-81. Results: Total effective rate: 94.12%. "It took 3-4 weeks to show an improvement in urinary dysfunction." "The shrinking of prostate size examined by ultrasound did not seem satisfactory; however, residual urine and urinary flow were very much improved, indicating this formula certainly normalizes the function of bladder sphincter and the musculature of the urethra. In other words, although the size of the prostate

	had not been significantly reduced, the distressful symptoms are markedly ameliorated." Dosing: one pack a day for 6-7 weeks. Each pack contained 15 gms of Hb. Epimedii. The administered composition (*Herba Epidemii*, commonly referred to as Horny Goat Weed) contains icariin which is a selective PDE V inhibitor under the Court's claim construction. Tr. 185:14-20; 186:3-13; 552:2-12; 555:1-24; 558:21-559:9.
excluding a compound selected from the group consisting of ….	Icariin is not within the excluded compounds of claim 1. Tr. 559:10-12.

UroPep does not contest that *Herba Epimedii* contains icariin or that icariin is a selective PDE V inhibitor under the Court's construction. Instead, UroPep argued that the formulation containing *Herba Epimedii* disclosed in Cheung is not a sufficient enabling disclosure of an "effective amount" of a selective PDE V inhibitor to treat BPH. However, an anticipating reference "need only 'be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention.'" *Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1371-72 (Fed. Cir. 2005) (quoting *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994)). Cheung clearly and credibly discloses a method using a formulation that included a selective PDE V inhibitor to effectively treat men suffering from BPH: 94% of the patients experienced improvement of their symptoms.

UroPep's attack on how much icariin would have to be used is really an attack on whether the composition disclosed in Cheung has commercial utility. However, the law does not require that the relevant anticipatory reference show or prove that the method was commercially viable. Unlike § 112 (which requires the specification to enable a person skilled in the art to

"use" the invention), § 102 "makes no such requirement as to an anticipatory disclosure." *In re Hafner*, 410 F.2d 1403, 1428 (C.C.P.A. 1969).

Further, in trying to discredit Cheung's disclosure of an effective amount of icariin, Dr. Bell compared it to the effective amount of ***5 mg of tadalafil*** that is approved by the FDA on the Cialis label to treat signs and symptoms of BPH. But the "effective amount" of a selective PDE V inhibitor in claim 1 of the '124 patent is ***not*** restricted to that of tadalafil (5 mg), as Dr. Bell had to admit. (Tr. 1308:20-1309:8.) In fact, there is no recitation anywhere in the claim as to a minimum dosage or range of dosage that would be an "effective amount." (Tr. 334:20-22.) Rather, as Dr. Bell admitted, an effective amount is simply the amount "that is therapeutically effective in the context of treating the disease." (Tr. 338:6-10.) This definition accords with Dr. Roehrborn's testimony. (Tr. 557:3-12.) The evidence established that the amount of icariin disclosed in Cheung is remarkably similar to the amount of zaprinast, which is specifically claimed as Claim 2 of the '124 patent. (Tr. 1321:3-1323:1; DX 1328.) Cheung's reported 94% improvement of symptoms is thus more than sufficient to meet any understanding of "effective amount," as well as to take into account any placebo effect. (Tr. 558:21-559:9; 574:1-7.) In fact, Cheung discloses significantly more evidence of the administration to a person of an effective amount of a selective PDE V inhibitor to treat BPH symptoms than is disclosed in the '124 patent. (Tr. 625:24-627:3.)

UroPep suggested that Cheung is unclear as to whether the formulation containing icariin was in fact given, or how many of the patients received it. But anticipation "requires only an enabling disclosure," not "actual creation or reduction to practice," so that "actual administration of [the drug] to patients [in the prior art] is irrelevant." *Schering*, 339 F.3d at 1380-81); *see also SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44 (Fed. Cir. 2005) (finding

chemical patent inherently anticipated, even though the inherently disclosed chemical was never actually proven to be produced); *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1371, 1375 (Fed. Cir. 2001); *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012).

UroPep also attempted to discredit Cheung because it discloses the use of herbal medicines (phytotherapy). But it is legally and factually uncontroverted that the '124 patent does not exclude phytotherapy. (Tr. 625:3-10.) The claim requires only the use of a compound able to selectively inhibit PDE V, and there was no dispute at trial that icariin, the ingredient in *Herba Epimedii*, is a selective PDE V inhibitor.

IX. ANY OF THE CLAIM CONSTRUCTIONS PREVIOUSLY PRESENTED BY THE PARTIES SUPPORTS JMOL IN LILLY'S FAVOR OR, IN THE ALTERNATIVE, A NEW TRIAL

As discussed above, Lilly is entitled to JMOL based on the claim constructions given by the Court to the jury, including those constructions given over Lilly's objections. In addition, adopting any of the parties' proposed constructions of the "inhibitor of phosphodiesterase (PDE) V" warrants JMOL in Lilly's favor: (1) if construed under § 112, ¶ 6, Lilly is entitled to JMOL because the trial record establishes that tadalafil is neither a disclosed nor equivalent structure; (2) if construed as proposed by UroPep during claim construction as "a compound able to inhibit PDE V" (i.e., with no selectivity requirement), Lilly is entitled to JMOL, for the reasons discussed above, that the claim as so construed is invalid for failure to meet the written description requirement or for lack of enablement; (3) if construed to require that selectivity be compared all known PDEs as of the filing date (i.e., PDE I to PDE VII), Lilly is entitled to JMOL for failure to meet the written description and enablement requirement, for the reasons discussed above and further based on UroPep's concession that because none of the disclosed compounds are 20-fold selective for PDE V versus PDE VI (Motions Hearing, Feb. 27, 2017, Tr.

19:3-12); and (4) if construed to require that selectivity be compared to all PDEs known as of the time UroPep made the narrowing amendment that the Court's to import "selective" as a limitation, Lilly is entitled to JMOL for the additional ground that the accused Cialis® product containing tadalafil does not infringe because it is not selective as to PDE I1A1 as shown by the Cialis label introduced at trial, PX 3 at Section 12.1.)

In the alternative, Lilly is entitled to a new trial on the grounds that the Court's claim constructions as provided to the jury, including its constructions of "prophylaxis," "a person in need thereof," "effective amount," and "inhibitor of phosphodiesterase (PDE) V," were erroneous.

X. EACH GROUND IN LILLY'S MOTION FOR JUDGMENT AS A MATTER OF LAW ALSO SUPPORTS A NEW TRIAL

If the Court denies Lilly's JMOL motion, Lilly submits that a new trial is warranted on each of the bases for JMOL on the grounds that, for each the reasons discussed above, the jury verdict rejecting Lilly's written description, enablement, obviousness and anticipation defenses was against the manifest weight of the evidence.

XI. A NEW TRIAL IS WARRANTED BECAUSE THE COURT'S JURY INSTRUCTION ON ENABLEMENT WAS ERRONEOUS

The Court should grant a new trial because it should have given Lilly's proposed instruction clearly advising the jury that the '124 patent's specification must enable a person of ordinary skill in the art to practice both the "prophylaxis" and "treatment" limitation. (Dkt. 359, p. 7.) There is no dispute that the method recited in claim 1 has two objectives stated in the alternative: "treatment" or "prophylaxis." ('124 patent, col. 8:18-19.) A person of skill in the art would understand that treatment and prophylaxis have different enablement requirements. (Tr. at 527:5-528:9.) "Prophylaxis" is not coterminous with "treatment" under Court's construction.

"Treatment" requires the disease to be present. "Prophylaxis," however, includes the "prevention of the . . . ***development*** of the disease." (Dkt. 131 at p. 10 (emphasis added); *accord* Tr. at 1412:2-3.) Dr. Roehrborn testified, without rebuttal, that the '124 patent did not enable a person of skill in the art to practice the prophylaxis element at all. (Tr. at 545:16-547:3.)

The Court rejected Lilly's proposed instruction because: (1) the focus of the evidence at trial, including the evidence supporting Lilly's invalidity defense, was on treatment (Dkt. 359, pp. 7-8); and (2) "the terms 'treatment' and 'prophylaxis,' as used in the '124 patent, do not describe distinct processes." (*Id.* at p. 8). Respectfully, Lilly submits that the trial record is to the contrary, clearly showing the difference between treatment and prophylaxis (e.g., Tr. at 527:5-24; 545:16-547:3) as well as based on the Court's construction of those terms (Tr. at 1412:4-9; *compare* Tr. 1412:2-3 (instruction on the "prophylaxis")). For example, "prophylaxis" can occur without an enlarged prostate or any lower urinary tract symptoms. By contrast, the Court's construction of "treatment" ***requires*** an enlarged prostate ***and*** "lower urinary tract symptoms":

> The term "treatment of benign prostatic hyperplasia" means "the treatment of the medical condition known as benign prostatic hyperplasia (BPH) or the symptoms of BPH." BPH is a condition in which an enlarged prostate results in lower urinary tract symptoms.

The Court's general instruction that the '124 patent must enable the "full scope" of claim 1 was not sufficient to inform the jury that the prophylaxis and treatment elements both needed to be enabled. A juror could have easily concluded that the presence of the word "or" in claim 1 meant that the claim was valid if either the treatment or prophylaxis elements were enabled, which is not the law. (Dkt. 359, p. 7 (agreeing with Lilly that a method for performing two objectives stated in the alternative requires the specification enable each of them).) Without Lilly's

proposed instruction, the jury could have improperly discounted Dr. Roehrborn's unrebutted testimony on the patent's failure to enable prophylaxis of BPH. A new trial is warranted.

XII. THE COURT'S REFUSAL TO INSTRUCT THE JURY THAT LAWS OF NATURE ARE NOT PATENTABLE PREJUDICED LILLY

"Laws of nature, natural phenomena, and abstract ideas are not patentable" under 35 U.S.C. § 101. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, __ U.S. __, 133 S. Ct. 2107, 2116 (2013) (quoting *Mayo Collaborative Servs. v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 132 S. Ct. 1289, 1293 (2012)). Although Lilly did not pursue a § 101 defense at trial, the Court should have given Lilly's requested instruction that the discovery of a law of nature is not, by itself, a patentable invention in order to provide the jury with the necessary framework to evaluate Lilly's defenses.

The need for such an instruction was particularly acute in light of the evidence that UroPep presented at trial. In response to Lilly's § 112 arguments, UroPep repeatedly asserted that the elements of the '124 patent were well known or readily ascertainable to persons of ordinary skill in the art as of the '124 patent's earliest effective filing date in 1997. To respond to Lilly's argument that the '124 patent does not describe common structural features or representative species of PDE V inhibitors, UroPep argued the '124 patent's named inventors did not invent any PDE V inhibitor because they were already well known in the art. (Tr. at 1283:8-10.) According to UroPep, the named inventors also allegedly did not need to identify the "effective amount" of any PDE V inhibitor because only "routine testing" was needed to determine that claim element. (Tr. at 1293:9-1294:12.) Nor, as urged by UroPep, did the named inventors have to teach how to identify "a person in need" of the claimed method or when any claimed PDE V inhibitor should be "administer[ed]." Rather, UroPep asserted all those steps

allegedly would have been easy for the treating clinician to ascertain on his or her own, without any guidance from the '124 patent. (Tr. at 222:24-223:2.)

The consequence of UroPep's attempt to demonstrate that the '124 patent had an adequate and enabling written description by resorting to the knowledge of a person of ordinary skill in the art was to concede that the '124 patent's named inventors had not actually "invented" anything patentable. According to the testimony of Dr. Uckert, the only named inventor who attended trial, the only contribution by the named inventors to the field was the discovery that PDE V plays a functional role in the prostate. (Tr. at 170:13-24.) The mere discovery that PDE V plays a functional role in the prostate, however, is not patentable. *See, e.g.*, *Myriad*, 133 S. Ct. at 2116. Nor was it the alleged invention of claim 1. The jury should have been given this knowledge of the law so it could understand that UroPep's response to Lilly's invalidity defenses was not a sufficient rebuttal.

Lilly had requested a § 101 instruction in each one of its jury instruction submissions. (E.g., Dkt. 250-2, pp. 19-20; Dkt. 317-1, p. 14.) Since the § 101 issues implicated all of Lilly's invalidity defenses, Lilly proposed introducing the concept early in the instructions as part of the discussion of inherent anticipation, including the following language:

> Let me give you an example. Humans lit fires for thousands of years before realizing that oxygen is necessary to create and maintain a flame. ***The first person to discover the necessity of oxygen certainly could not have obtained a valid patent claim for a method of making a fire by lighting a flame in the presence of oxygen***. Even if prior art on lighting fires did not disclose the importance of oxygen and one of ordinary skill in the art did not know about the importance of oxygen, ***understanding this law of nature would not give the discoverer a right to exclude others from practicing the prior art of making fires***.

(Dkt. 317-1, p. 14 (emphasis added).) During the charge conference, Lilly's counsel specified this language as the § 101 instruction that Lilly was proposing. (Tr. at 1366:16-19.)

The Court ultimately rejected providing any instruction that conveyed to the jury that a law of nature was, by itself, not a patentable invention. In its post-trial Order, the Court gave three reasons why it rejected Lilly's proposed instruction regarding the unpatentability of laws of nature. First, the Court noted that Lilly was not pursuing a § 101 defense at trial. (Dkt. 359, p. 13.) That was true, but Lilly did not propose that the jury be instructed on a § 101 defense. Lilly only asked that the jury be informed that laws of nature were not patentable so that it could properly evaluate UroPep's attempt to rebut the invalidity defenses that Lilly was pursuing.

Second, because Lilly had presented its proposed instruction as part of the inherent anticipation instruction, the Court indicated that it viewed the language as "related to the role of inherency in the law of anticipation, not to the principle that a natural phenomenon cannot be patented." (Dkt. 359, p. 13 n.5.) The statement that "understanding this law of nature [that fires need oxygen to burn] would not give the discoverer a right to exclude others from practicing the prior art of making fires," however, is not a description of the doctrine of inherent anticipation. (Dkt. 317-1, p. 14.) That is a real-world example of the principle enunciated in *Myriad*, 133 S. Ct. at 2116. As noted above, Lilly proposed adding it to the inherency section so that it would appear early in the invalidity instructions as it affected each of the invalidity defenses.

Third, the Court focused on two statements made by Lilly's counsel during the charge conference and stated that they, standing alone, would not have been proper instructions. (Dkt. 359, pp. 13, 14.) These statements, however, were not the instruction that Lilly requested but were simply responsive to statements made by UroPep's counsel. (Tr. at 1361:9-1365:8; 1366:16-1367:4; Dkt. 317-1, p. 14.)

The decision not to give the requested instruction that a law of nature is not patentable affected each of Lilly's invalidity defenses, but most of all Lilly's anticipation and obviousness

defenses. The jury was allowed to credit UroPep's argument that the mere discovery that PDE V played a functional role in the prostate was sufficient to sustain the validity of claim 1 over the Cheung reference and the other prior art. But the mere discovery that PDE V played a functional role in the prostate was not, standing alone, enough to get a patent. Indeed, it did not even accurately reflect the language of claim 1. A new trial is warranted for this reason as well.

XIII. A NEW TRIAL IS WARRANTED BECAUSE THE COURT EXCLUDED EVIDENCE AND PREVENTED IMPEACHMENT TESTIMONY THAT PREJUDICED LILLY

A new trial is also warranted because the Court erred in excluding Lilly Trial Exhibits 1413 and 1414 (the "Bunnage references"). Lilly renews its pre-trial arguments that this conclusion was in error. (Dkts. 256, 292.) Among other things, the Bunnage references were relevant to Lilly's obviousness claim as it reflected, at a minimum, a simultaneous invention of the use of a PDE V inhibitor (sildenafil) to treat BPH. (Dkt. 256, pp. 1-6.) The Bunnage PCT Application had been identified in Lilly's Invalidity Contentions and the Local Rules did not require Lilly to disclose detailed factual bases for secondary considerations of non-obviousness. Dr. Bell both recognized and provided deposition testimony regarding the Bunnage references. At a minimum, the Court should have admitted the Bunnage PCT Application, which had been specifically identified in Lilly's Invalidity Contentions.

In addition, Lilly should have been permitted to impeach Dr. Bell's false testimony at trial that Pfizer scientists first started considering sildenafil or sildenafil-based compounds as a treatment for BPH "in September 1997." (Tr. at 349:15-20.) This was directly inconsistent with Dr. Bell's testimony in his deposition, where he admitted that Pfizer first considered sildenafil as a treatment for BPH at least as early as April 1997. (Dkt. 256, pp. 1-6; Dkt. 256-2, Bell Dep., pp. 65:17–70:14.) In addition, Dr. Bell was asked at trial: "Do you have any information that Pfizer

scientists were looking at using sildenafil to treat BPH before September of 1997?" (Tr. at 349:23-25.) Dr. Bell answered "No." (Tr. at 350:1.) That testimony also was false. As noted, Dr. Bell had information that Pfizer scientists were looking at using sildenafil to treat BPH before September 1997 based on, at a minimum, his knowledge of the Bunnage references from his deposition. Once Dr. Bell provided inaccurate testimony in response to Lilly's question, the Court should have allowed Lilly to impeach him with his deposition testimony, which clearly established that he did have information that Pfizer scientists were looking at using sildenafil to treat BPH before September 1997. At a minimum, Lilly should have been permitted to use the Bunnage references or Dr. Bell's deposition testimony to refresh his recollection and get the correct date in the record.

The effect of the Court's decision both to exclude the Bunnage references and preclude Lilly from using either them or Dr. Bell's prior deposition testimony was substantial. UroPep later conducted an extensive cross-examination of Dr. Rotella based on the premise that use of a PDE V inhibitor as a treatment for BPH was unknown to anyone other than the '124 patent's named inventors in 1997 and for many years later. (Tr. at 798:6-814:9, 821:9-824:3.) In closing argument, UroPep's counsel argued that the assertion that the argument that it was obvious to use a PDE V to treat BPH was solely the product of hindsight analysis. (Tr. 1444:21-1446:17.) UroPep unfairly took advantage of the Court's exclusion of the Bunnage references and Dr. Bell's inaccurate testimony to promulgate the myth that only the '124 patent's named inventors were considering the use of PDE V inhibitors to treat BPH in 1997. That was improper and prejudicial to Lilly. A new trial is warranted.

XIV. A NEW TRIAL IS WARRANTED BECAUSE THE COURT'S ERROR IN PERMITTING UROPEP'S CROSS-EXAMINATION OF DR. ROTELLA ON THE '368 PATENT WAS PREJUDICIAL

The Court overruled Lilly's pre-trial objection to UroPep's use of the '368 patent (PX 189) to cross-examine Dr. Rotella. (Dkt. 264, pp. 2-6.) Lilly renews its prior arguments. The '368 patent's disclosure and claims are unlike the '124 patent's disclosure and claims. Among other things, the '368 patent is limited to compounds having a specified chemical structure whereas the '124 patent is not. (Dkt. 252, pp. 7-13.) Moreover, the disclosure and claims of the '368 patent are irrelevant to whether the '124 patent is valid. Claim 1 of the '124 patent stands and falls on its own, based on the '124 patent's disclosure, not based on the disclosure of some other patent. *Id.* Lilly warned that admitting the '368 patent would result in a lengthy side-show and irrelevant distraction for the jury. *Id.*

Lilly's concerns and warnings were prophetic as UroPep again took advantage of the Court's ruling to press this matter well beyond proper cross-examination. UroPep's lengthy cross-examination of Dr. Rotella was dominated by questioning on the '368 patent to improperly bolster the validity of the '124 patent. (*See* Tr. at 798:6-802:1, 821:9-824:3, 829:14-859:12.) UroPep implied that the absence of BPH from the '368 patent demonstrated that the UroPep researchers were the only ones who considered using PDE V inhibitors to treat BPH prior to July 1997 (they were not, as Dr. Bell knew well). UroPep misleadingly suggested that the '368 patent's ***structurally*** defined genus of compounds was the same as the '124 patent' ***functionally*** defined genus of compounds. UroPep's counsel even cited the '368 patent to ask Dr. Rotella, "do you think our patent system should have one rule for pharmaceutical companies and another one for small startups in Germany?" (Tr. at 858:13-15), a theme that it returned in its closing argument (Tr. at 1494:24-1495:3).

In this short, five-day trial, this extensive focus on the '368 patent to improperly bolster the validity of the '124 patent loomed disproportionately large. It was confusing to the jurors and prejudicial to Lilly, who could not hope to teach the jurors the needed principles of advanced medicinal chemistry or patent law to understand the defects in UroPep's facile arguments. The Court's vision of a limited, targeted use of the '368 patent when it allowed UroPep to use it at trial (Dkt. 264, p. 6) was instead blown up into the irrelevant and prejudicial mini-trial that Lilly feared. A new trial is warranted.

XV. CONCLUSION

For all or any of the foregoing reasons, claim 1 of the '124 patent is invalid under 35 U.S.C. §§ 102, 103, and/or 112. JMOL should thus be entered in Lilly's favor. In the alternative, the Court should order a new trial, as the verdict on the validity issues is against the weight of the evidence, or a new trial for the additional reasons identified herein.

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a). As such, this document was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A). Pursuant to Fed. R. Civ. P. 5(d) and Local Rule CV-5(d) and (e), all other counsel of record not deemed to have consented to electronic service were served with a true and correct copy of the foregoing by email and/or fax, on this the 15th day of June, 2017.

/s/Todd G. Vare